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## ANTICOAGULANT TREATMENT OF POSTOPERATIVE VENOUS THROMBOSIS AND PULMONARY EMBOLISM\*

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BOSTON

ANTICOAGULANT treatment is winning for itself a firm place in the armamentarium against postoperative venous thrombosis and pulmonary embolism. This has been accomplished by the sheer weight of accumulating statistics from various clinics, both in this country and in Sweden.<sup>1-22</sup> Since April, 1941, when dicumarol first became available, the drug has provided the predominant method of therapy at the Lahey Clinic. In the majority of cases a combination of heparin and dicumarol has been used. During the first four years heparin was given by continuous intravenous drip to cover the latent period of dicumarol. For the past two years deep injections of Loewe's<sup>22,21</sup> heparin in Pitkin menstruums<sup>9</sup> have been given subcutaneously.

In this series of 184 cases, occurring from 1942-1946, venous ligation was also performed in 10 cases. The two systems of treatment, venous ligation and administration of heparin in Pitkin menstruum, should not be considered rival methods but rather complementary to each other. Our confidence in the efficacy of anticoagulant therapy, however, has grown through these five years to such an extent that the indications for venous ligation have dwindled to the following conditions: hemorrhagic disease, severe liver disease, second-stage operation, ambulatory phlebotrombosis with pulmonary embolism (Homans), resistance to both heparin and dicumarol, recurrence of benign embolism after supposedly adequate treatment, prophylactic ligation in patients over sixty years of age for expected bleeders (prostatic resection), and prophylactic ligation in patients over sixty who are debilitated from cancer or other causes (Miles resection). Ligation in elderly patients who are debilitated from cancer or other causes is regarded as only a rela-

tive indication to be used at the surgeon's judgment, because in the Lahey Clinic it would add the insurmountable surgical burden of about three or four thousand ligations a year. Therefore, prophylactic exercises, early ambulation and dicumarol prophylactically are preferred on the fourth day after operation.

Although it must be admitted that the vagaries of dicumarol resistance and sensitivity in different patients and the pitfalls of accurate prothrombin estimations should limit its use to the experienced and wary clinician equipped with a very reliable laboratory, it is believed that the advent of heparin in Pitkin menstruum will popularize anticoagulant therapy as a safe and reliable method of treatment. This will occur when the menstruum is more widely available and the cost of this product has dropped. Loewe<sup>21</sup> now claims that more careful buffering of the menstruum has overcome the frequent painfulness of the deposit in the tissues. This makes it possible to give more numerous injections than when heparin in Pitkin menstruum is combined with dicumarol. Up to the present time we have not had the opportunity of using this allegedly more painless formula. Unless the production of pain can be overcome, protracted treatment with many injections will be limited.

After five years' experience with anticoagulant therapy we have evolved the following set of rules—applicable to all patients kept lying in bed—for instruction to the staff:

As a precaution against thrombosis and embolism, the patient should be instructed to wiggle the toes and feet one thousand times daily, including pressing the soles of the feet against the foot of bed if possible.

If the patient has varicose veins, elastic bandages are to be used twenty-four hours a day until he is ambulatory.

The patient should be asked daily on rounds if there is pain in the calf, and inspected for sore-

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ness in the calf and for Homans's sign, especially if unexplained fever is present

A stamp has been provided for history charts, entitled "History of Venous Thrombosis or Pulmonary Embolism" This should be stamped on every history and filled in. If a patient with such a history comes to surgery, he should re-

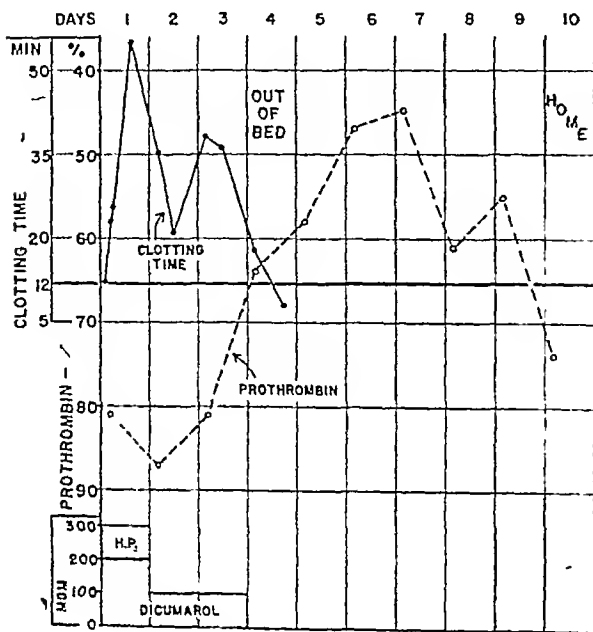


FIGURE 1 Course in a Typical Case Successfully Treated with Anticoagulants

Any part of the coagulation time above the heavy black horizontal line represents the anticoagulant effect of heparin, any part of the prothrombin line above the same black line represents what is considered a fairly safe antithrombotic effect of dicumarol—namely, a prothrombin level below 65 per cent. We strive to keep the prothrombin percentage between 40 and 50.

ceive postoperative anticoagulant therapy after consultation between the surgical and medical departments

Such treatment should be started routinely four days after operation, five days after gall-bladder surgery or on a later day if deemed advisable by the surgeon. Dicumarol only is necessary for such prophylactic therapy, and therefore only the prothrombin time should be determined.

No anticoagulant therapy is given to patients with severe liver disease or hemorrhagic diseases or to those who are soon to undergo a second operation.

The routine after carotid-artery ligation, immediately after return from the operating room, includes 100 mg of heparin in Pitkin menstuum without a vasoconstrictor, 100 mg of heparin in Pitkin menstuum with a vasoconstrictor and 200 mg of heparin in Pitkin menstuum with a vasoconstrictor if the patient weighs over 150

pounds. Only one such injection, deep subcutaneously, should be given, and no coagulation-time control is necessary.

For routine anticoagulant therapy, the prothrombin and coagulation times should be controlled.

Heparin in Pitkin menstuum—100 mg—without a vasoconstrictor and heparin in Pitkin menstuum—100 mg—with a vasoconstrictor should be injected deep subcutaneously, if the patient weighs over 150 pounds, 200 mg with a vasoconstrictor should be injected deep in the subcutaneous tissues.

Dicumarol (200 mg) should be given—300 mg if the patient weighs over 150 pounds.

Daily morning determinations of the coagulation time and prothrombin percentage are necessary.

A daily maintenance dose of 50 to 100 mg. of dicumarol should be administered to keep the prothrombin between 50 and 60 per cent.

No dicumarol should be given until the morning prothrombin time is known for that day.

If the patient proves refractory to dicumarol, the same dosage of heparin in Pitkin menstuum should be given until the coagulation time comes back to normal, usually every third day.

Heparin in Pitkin menstuum should be discontinued when the prothrombin drops to 60 per cent, and coagulation-time determinations should be stopped.

For any bleeding, the prothrombin time, as well as the coagulation time if the patient is also receiving heparin, should be determined, and 60 mg of vitamin K given intravenously. This procedure is repeated every six hours until the prothrombin time is normal, which takes from eight to forty-eight hours. Fresh-blood transfusions should be given if indicated to give undeteriorated prothrombin. A transfusion is needed to counteract the effect of the heparin, and vitamin K to counteract that of dicumarol. Ice bags should be applied to the heparin in Pitkin menstuum deposit.

The patient is to be ambulatory when the temperature has returned to normal and local signs of venous thrombosis (except swelling) have disappeared, if the surgical department permits and if the anticoagulant effect is present.

Paravertebral sympathetic blocks should be employed if signs of reflex arterial spasm (swelling, white limb, absent pulses and pain) are present.

A heat cradle should be applied to the legs.

For pulmonary embolism, 0.6 to 0.12 gm of papaverine should immediately be injected intravenously.

Figure 1 illustrates a typical successfully treated case. A majority of patients in this series were

allowed out of bed within ten days of the beginning of therapy

The fact that anticoagulant therapy can do nothing to prevent the fragile red clot of phlebothrombosis from breaking off is the chief argument advanced by the opponents of this method of treatment. Three facts assure protection against this hazard. Loewe,<sup>22</sup> in a recent communication, has shown that heparin actually causes this "sludge" type of clot to disappear in animal experiments *in vivo* (whether dicumarol actually has a similar effect has never, to our knowledge, been proved), statistics have accumulated to prove that the actual subsequent pulmonary emboli to be expected statistically do not occur, and metastasis of the bland phlebothrombosis clot results from very fresh, unrecognized foci and rarely from clinically recognizable foci. Such dangerous new areas of phlebothrombosis are prevented from forming.

Death from pulmonary embolism is also made less likely by the prevention of propagation of a thrombus already present in the pulmonary arterial tree. This fact leads to the rule of permitting patients to be out of bed only when a good anticoagulant effect obtains.

The advantages of anticoagulation are as follows: avoidance of another operation, usually on a very sick patient; avoidance of danger of swelling in some cases; avoidance of danger of arterial thrombosis and gangrene in arteriosclerotic patients; inhibition of spreading thrombotic disease in systemic veins and in pulmonary arteries if a benign embolism has already occurred; no hesitation to institution of anticoagulant therapy in very doubtful cases; statistical proof from several clinics that anticoagulation prevents subsequent fatal pulmonary embolism, and decreased incidence of postphlebotic venous stasis and ulcer (Bauer<sup>23</sup>).

### RESULTS

There were 184 cases of postoperative venous thrombosis with or without pulmonary embolism during the five years 1942-1946. Sixty-three patients received heparin intravenously, 2 of them by the intermittent, Swedish method. Fifty-five received heparin in Pitkin menstruum. One to five injections of heparin in Pitkin menstruum were necessary according to the patient's refractoriness to dicumarol. Three patients received heparin only. Sixty-three patients received dicumarol only. Twenty-seven patients, or 15 per cent, were considered refractory to dicumarol. All such patients now receive heparin in Pitkin menstruum to keep them in control. A patient was considered refractory when the prothrombin level did not fall below 65 per cent despite ordinarily adequate doses. Fortunately, only 1 death occurred among the refractory patients, but this is not considered an excuse to administer dicumarol without adequate control

of dosage by determination of the daily prothrombin levels.

Sixty-one of the 184 patients, or 33 per cent, had a warning benign pulmonary embolism (Table 1). To the 184 cases must be added 54 patients who had postoperative pulmonary embolism and who died untreated, because such deaths either occurred suddenly or were unrecognized as thrombosis with embolism. This makes a total of 238 cases of thromboembolic disease in five years, or an incidence of 0.42 per cent among approximately 56,000 major surgical operations performed at the New England Deaconess and New England Baptist hospitals by the surgeons of the Lapey Clinic. This low incidence

TABLE 1 *Incidence of Venous Thrombosis and Pulmonary Embolism among 56,000 Major Surgical Operations (1942-1946)*

POSTOPERATIVE COMPLICATION	NO. OF CASES
Venous thrombosis without embolism (treated)	123
Venous thrombosis with warning pulmonary embolism (treated)	61
Sudden or unrecognized fatal pulmonary embolism (not treated)	54
Total	238 (0.42%)

was due to the assiduous care of the nursing staffs of these two hospitals in seeing that the patients carried out proper prophylactic exercises. That such precautions were largely responsible for the results is strongly suggested by the fact that in three winter months at the start of our campaign against pulmonary embolism the incidence in a hospital where the staff had not yet received instructions to carry out these exercises was three and a half times that in another hospital, where the exercises were practiced, the number of cases being 7 and 2 respectively.

There were 6 fatal cases in the series of 184 patients. Two were postoperative chemical deaths. One patient early in the series died of hemorrhage from dicumarol poisoning, because at that time the value of the rule never to give the daily dose of dicumarol until that morning's prothrombin time is known was not appreciated. This leaves 3 fatal cases of thromboembolic disease. One patient received inadequate doses of dicumarol, and a prothrombin level within the therapeutic range was never obtained; he was also given a transfusion, which destroyed any slight effect the dicumarol might have had, and he died of a second pulmonary embolism a few hours later. Another patient died a few hours after a single pulmonary embolism, in spite of one dose each of heparin in Pitkin menstruum and dicumarol given when he was in extremis. He would not have been saved by venous ligation, unless it had been done prophylactically at the time of operation. The cause of death in the

third case was declared sepsis by the pathologist. The patient had received adequate anticoagulant control throughout, but died of a septic infarct with pyopneumothorax and septic peritonitis.

It has long been recognized that a warning benign pulmonary embolism increases greatly the chance of a subsequent fatal embolism. In all 3 fatal cases a warning embolism had occurred. There were 61 cases in the series in which a warning was given by a benign infarct to the lung—a mortality of 5 per

cent never had a warning infarct. This fact points up the danger to the patient who has had a warning embolism.

### COMPLICATIONS

Bleeding was recorded in 12 cases (Table 2). It was of a serious nature, requiring transfusions or vitamin K, or both, in 5. Two cases required heroic treatment with repeated doses of 60 mg of vitamin K and transfusions totaling as much as 2750 cc of blood. There was 1 fatal case of bleeding into the wound early in the series before vitamin K was known to be an antidote for dicumarol.

Vitamin K has made dicumarol much safer to use. For prothrombin levels as low as 20 per cent, we have often given booster doses of 40 mg of vitamin K (either Hiquinone or Synkavite), bringing the prothrombin level to a safer therapeutic range but not losing the anticoagulant effect. For serious

TABLE 2 Complications of Anticoagulant Therapy

COMPLICATION	No. OF CASES
Serious bleeding requiring vitamin K, or transfusions, or both with recovery	4
Death from bleeding into wound from dicumarol poisoning	1
Epistaxis from ulcer on Hesselbach's triangle requiring cauterization	1
Bleeding from various sources not requiring treatment	6
Total	12

cent in this category, or 1.6 per cent for the entire series. In the past two years, since the use of heparin in Pitkin menstruum as well as dicumarol and with better control of the anticoagulant effect by continued administration of heparin subcutaneously until a good dicumarol effect is obtained, only 1 death has occurred—that of the patient with sepsis mentioned above.

There were benign recurrences of pulmonary embolism in 2 of the 61 patients who had warning

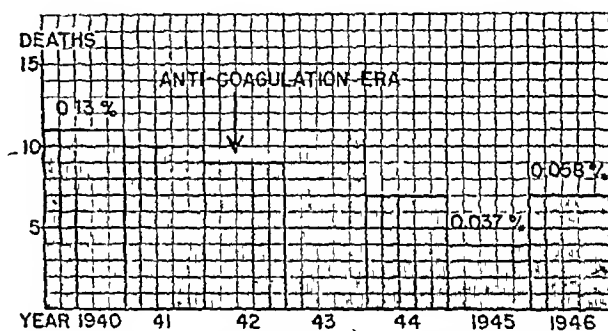


FIGURE 2 Mortality from Postoperative Pulmonary Embolism. Note the decreasing rate after institution of anticoagulant therapy, in 1942, together with institution of prophylactic exercises and increased watchfulness for signs of thromboembolic disease.

TABLE 3 Warning Signs in 52 Fatal Cases of Pulmonary Embolism (1940-1945)

TYPE OF CASE	No. OF CASES	WARNING SIGNS* NO. OF CASES
Death in 1 hour	22	16
Death in 2-24 hours	20	18
Death 1-24 days after first benign pulmonary embolism	10	10

\*Warning signs included fever and tachycardia, varicose veins, previous history of thrombosis or embolism and premonitory pulmonary embolism.

benign pulmonary infarcts. One of these occurred after only four days and after treatment had been abandoned. Further heparin in Pitkin menstruum combined with dicumarol was given, with recovery. In the other patient dicumarol had also been stopped when a subsequent embolism occurred. Bilateral ligation was then performed, with recovery. The prothrombin level at the time of infarct was not stated in the records of either patient.

There was no occurrence of either fatal or benign pulmonary infarct among the 123 patients who

bled; we recommend 60 mg intravenously, repeated two or three times a day, together with transfusions of fresh citrated blood. Bank blood is too low in prothrombin content but may be used for blood replacement. We have had no experience with protamine as an antidote for heparin.

There has been no incidence of hematomas at the site of injection of heparin in Pitkin menstruum in over 55 patients receiving eighty-three injections.

### DISCUSSION

There still remains the problem of the sudden deaths from pulmonary embolism occurring before there is an opportunity to treat the patient. The results reported above give us great confidence in trusting anticoagulant therapy in the recognized cases of postoperative venous thrombosis. During the five years under study 59 patients died of pulmonary embolism, in 27 the diagnosis was proved at autopsy, 4 cases in this category occurring in medical patients. This situation must be met by eternal watchfulness of the postoperative and bed-

ridden patient. Here, too, lies a field for more prophylactic ligations as done by Allen, Linton and Donaldson<sup>26</sup> in the debilitated patient over sixty years of age. Dicumarol should be used prophylactically more often, and we give this treatment routinely to patients with a history of thrombophlebitis or embolism following a previous operation or childbirth. Our results in the prophylactic use of dicumarol will be the subject of a future report.

In addition to the routine daily examination of legs postoperatively, more attention must be paid to the temperature and pulse chart. A recent analysis of 52 cases of death from pulmonary embolism revealed that 85 per cent of the patients gave warning signs of rise in temperature or pulse, or both, or had varicose veins or a previous history of thrombotic disease (Table 3).<sup>8</sup>

That our efforts to prevent death from postoperative pulmonary embolism have not been in vain is shown in Figure 2. The mortality was cut to one fourth in 1945 and to one half in 1946. The rise during the last year shows the need of guarding against complacency and of still greater alertness on the part of all services to attain what should no longer be considered an impossibility: a deathless year from pulmonary embolism. More prophylaxis by both venous ligation and anticoagulation seems to be the answer. The former is impractical in a large surgical service except in cases considered most susceptible. Prophylactic exercises, bandaging of varicose veins, early ambulation and anticoagulant therapy must be used for the larger majority of patients considered to be susceptible. Anticoagulant therapy is adequate for postoperative patients who already have developed thrombosis with or without pulmonary embolism.

### SUMMARY

Anticoagulant treatment by heparin or heparin in Pitkin menstruum in combination with dicumarol offers a safe, practical method to prevent postoperative death from pulmonary embolism.

The recent introduction of heparin in Pitkin menstruum injected subcutaneously has greatly simplified anticoagulation. This therapy has the added advantage of producing an anticoagulative effect that can easily be kept up as long as necessary in the dicumarol-refractory patient.

Of 184 patients with postoperative venous thrombosis with or without warning pulmonary embolism, 3 patients died of thromboembolic disease — an incidence of 1.6 per cent. These 3 deaths occurred in the particularly dangerous group of cases in which the patients had already suffered one pulmonary embolism, and represented a mortality of only 5 per

cent in this category. On analysis, none of these 3 cases presented a clear-cut argument against the efficacy of anticoagulation therapy.

Since 85 per cent of patients with fatal pulmonary emboli give warning signs, usually a low temperature and tachycardia or a history of previous thromboembolic disease, or have varicose veins, a plea is made for better prophylaxis. This can be accomplished by leg exercises, bandaging of limbs, early ambulation, prophylactic ligation in debilitated patients over sixty years of age or the administration of dicumarol on the fourth day after operation.

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## THIOURACIL AND ALLIED DRUGS IN HYPERTHYROIDISM\*

ELMER C BARTELS, M D †

BOSTON

THE introduction by Astwood of new and potent antithyroid substances has permitted a great advance in the treatment of hyperthyroidism and has given a new tool with which to further knowledge of the pathological physiology of diseases of the thyroid gland. This report deals with the clinical application of these drugs, which are capable of reducing to normal the elevated basal metabolic rate of hyperthyroidism resulting from either primary hyperthyroidism or adenomatous goiter. With the fall in the basal metabolic rate there is gradual amelioration of all hyperthyroid signs and symptoms except those of the eye, if these signs are marked when therapy is begun. Those who have had experience with the use of thiouracil and allied drugs must now report their results so that proper evaluation can be made. Particularly, the early overoptimistic statements regarding their supposed curative properties must be assayed.

## ACTION

When the drugs are administered in adequate doses, the production of thyroxin is halted as shown by a reduction in the blood protein-bound iodine and in the iodine content of the thyroid gland. The basal metabolic rate drops, and if the agent is continued sufficiently long, myxedema results and is maintained as long as the drug is given. Unlike the antithyroid action of iodine, which produces striking histologic improvement in the thyroid gland in primary hyperthyroidism with lessening of symptoms, thiouracil and its allied substances, although affording striking effects upon the clinical and metabolic picture, cause no change in the histologic picture. The hyperplasia of the thyroid gland may even increase. In determining whether or not these drugs will provide a substitute for subtotal thyroidectomy, it must be recognized that the histopathologic change (hyperplasia), which originally brings about hyperthyroidism, is still present even after the basal metabolic rate has been effectively restored to normal.

It was initially supposed that these drugs acted by preventing the thyroid gland from absorbing iodine. Clinical experience, however, revealed this to be incorrect, since it was found that the administration of Lugol's solution produced involution of the thyroid gland even when thiouracil was being administered. This was demonstrated by an in-

crease in the firmness of the gland, a lessening or disappearance of the bruits and thrills at the superior poles and a marked reduction in the vascularity of the gland at operation in patients receiving Lugol's solution in conjunction with thiouracil. A comparison of patients receiving thiouracil alone and those receiving both thiouracil and iodine showed that there was substantially more iodine in the thyroid glands of the latter (Fig 1). It was then reported by McGinty and Sharp<sup>2</sup> that the iodine absorbed by additional iodine feeding to rats receiving thiouracil or propylthiouracil is not synthesized into a protein-bound form but remains in the gland as iodide. This indicates that these antithyroid substances act by preventing the synthesis of iodide to an active protein-bound hormone — diiodotyrosine and thyroxin (Fig 2). The thiocyanate ion, on the other hand, has a specific effect upon the thyroid gland in that it interferes with the mechanism that permits the gland to hold the iodide ion and does not seem to interfere with the synthesis of the thyroid hormone.<sup>3</sup>

The selective mechanism by which thiouracil and its allied substances interfere with the organic blending of iodide is as yet not certain. Studies by DeRobertis<sup>4</sup> warrant the conclusion that these substances probably act by inhibiting the peroxidase or enzymatic system in the thyroid gland that functions to oxidize iodide to form the protein-bound or active thyroxin molecule.

## DOSAGE

The effective daily dose of thiouracil was established from the very outset to be 600 mg. Thiobarbital, which was next given a therapeutic trial, was found to affect the metabolism beneficially in a single dose of 50 mg a day. The dose of propylthiouracil, which was initially suggested as 50 to 100 mg daily, was found to be inadequate, since it did not produce a response comparable to that obtained with a daily dose of 600 mg of thiouracil. Some patients responded to 75 mg a day, but it was not until the daily dose had been increased to 200 mg that uniformly satisfactory improvement was accomplished in all cases. Larger doses, up to 600 mg a day, have been used in a few cases without a significant difference in clinical response to that obtained with 200 mg. For patients with large adenomatous goiters, whose response to therapy is always slow, a daily dose of 300 mg is given.

Propylthiouracil, the drug that we now employ exclusively, is administered in a dosage of 100 mg.

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every twelve hours (100 mg at 8 a.m. and 100 mg at 8 p.m.) In a few patients the entire dose, 200 mg, was administered once a day with a clinical response that was as effective as that to the divided doses.

### Toxicity

Since the three agents with which we have had experience are equally effective in lowering the basal metabolic rate, the choice of agent for clinical use is dependent on the percentage of reactions to each. Of the three, thiobarbital had the highest incidence of complications, 28 per cent, thiouracil, 9 per cent, and propylthiouracil is much the safest, 1.6 per cent, or six reactions in 430 cases.

The reactions to thiouracil consisted of depression of the white-cell count, fever, swollen salivary glands, skin rash and edema of the skin, with 1 fatal case of agranulocytosis. Thiobarbital primarily affected the white-cell count and occasionally caused fever. The six definite reactions to propylthiouracil included depression of the white-cell elements in 5 patients and fever in 1, the blood changes were variable (Fig. 3), comprising granulocytopenia without leukopenia, or leukopenia without granulocytopenia and various degrees of depression of both the leukocytes and granulocytes. One patient developed agranulocytosis, this patient recovered after penicillin therapy. These experiences indicate that propylthiouracil is by far the safest drug but force the conclusion that it is not entirely unattended by significant side effects.

### REMISSION AND RELAPSE

It was hoped by all and prematurely reported as established by some that these new drugs had, in

was suggested as a means of effecting the desired result. Wider experience by many physicians soon indicated that prompt relapse of hyperthyroidism followed a reduction of the dose or withdrawal of

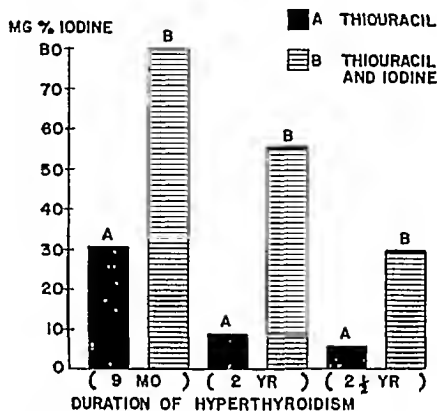


FIGURE 1 Comparison of the Iodine Content of the Thyroid Gland following the Administration of Thiouracil with That following the Administration of Combined Thiouracil and Iodine (Reproduced from Lukry et al. by Permission of the Publishers)

the drug in many cases, irrespective of the duration of active therapy. In other cases prolonged remissions occurred after discontinuance of treatment. The percentage of remissions produced and the percentage of relapses vary widely in the available

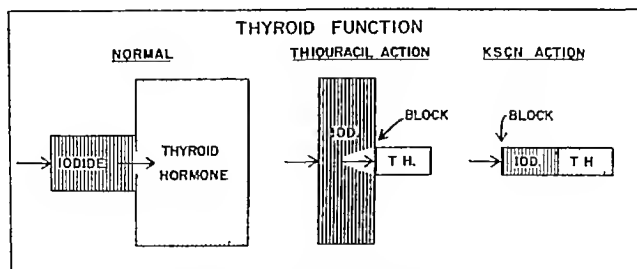


FIGURE 2 Schematic Comparison of the Normal Thyroid Function as Affected by Thiouracil and Potassium Thiocyanate

addition to the capacity to reduce the basal metabolic rate to normal, the property of producing a sustained remission of hyperthyroidism in a high percentage of patients. A year of continued therapy

reports. My experience indicates that prolonged remission (we prefer to designate the hyperthyroid-free period as remission and not cure) occurs in some patients with mild hyperthyroidism in whom

the thyroid enlargement is but slight and that the duration of treatment has little to do with the duration of the remission so long as the basal metabolic rate is normal when the drug is withdrawn (Fig 4). Likewise, relapse in two to six months was observed after reduction of the dose or on withdrawal of antithyroid therapy in patients with a high degree of hyperthyroidism and sub-

primary hyperthyroidism and adenomatous goiter under antithyroid treatment. Actually, the basic etiologic cause of hyperthyroidism must be determined before the occurrence of relapse or remission of hyperthyroidism as affected by antithyroid therapy is understood.

### MAINTENANCE THERAPY

The use of antithyroid drugs as maintenance treatment, which is necessary in a high percentage of cases if medical treatment is to be utilized and thyroidectomy avoided, carries with it certain specific disadvantages. It must, however, be admitted that by a carefully regulated daily dose of these drugs, hyperthyroidism can be adequately controlled for a prolonged period. Proper regulation

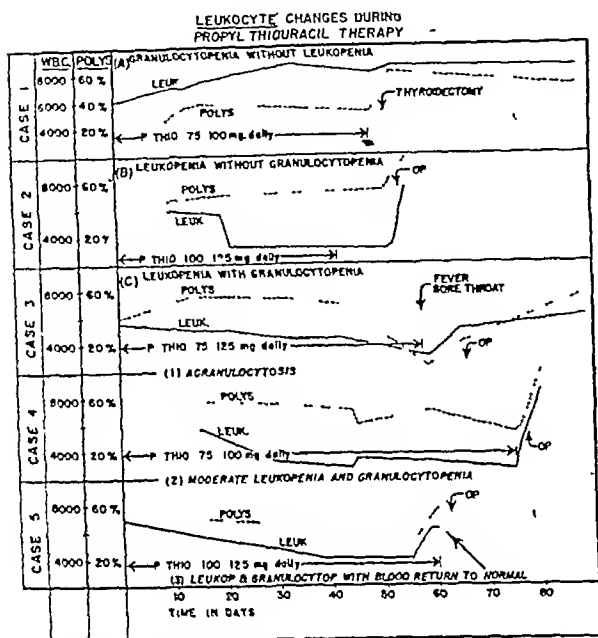


FIGURE 3 Significant Changes in the Total White-Cell Count and Polymorphonuclear Percentage during the Administration of Propylthiouracil (Reproduced from Bartels<sup>6</sup> by Permission of the Publishers)

stantial thyroid enlargement, in spite of prolonged therapy (Fig 5).

Since a large proportion of the patients who are referred to the Lahey Clinic for care have severe hyperthyroidism, a program of treatment aimed at inciting a remission would hold little chance for success. Whether the recently suggested plan of producing hypothyroidism before withdrawal of treatment<sup>7</sup> will result in a higher percentage of remissions or in more prolonged remission, only further observation will decide. From the histopathological standpoint, since the enlarged thyroid gland is present and still hyperplastic and the adenomatous gland remains as before, it is expected that this plan would only delay the inevitable relapse that follows. It has been reported that prolonged treatment leads to exhaustion and atrophy of the thyroid gland. We have observed the gland to decrease in size in a few patients with mild hyperthyroidism with only slight thyroid enlargement who have remained in prolonged remission. We have also observed, however, substantial increases in the size of the thyroid gland of patients with

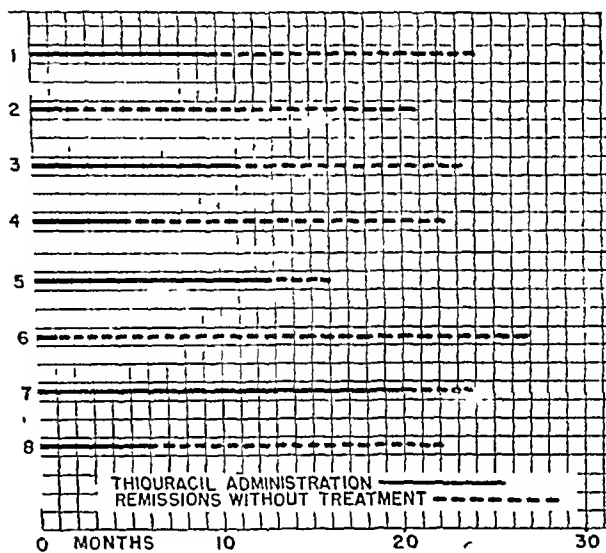


FIGURE 4 Prolonged Remission after Treatment with Thiouracil in Mild Hyperthyroidism with Slight Thyroid Enlargement (Reproduced from Bartels<sup>6</sup> by Permission of the Publishers)

entails periodic observations, which must include determination of basal metabolic rates and blood studies, and in the event of intercurrent illness further adjustment of the dose may become necessary, as with insulin therapy in diabetes. There are many serious objections to permitting patients to continue in a state of only partial control of hyperthyroidism, especially patients in the older age group, those with associated heart disease and those patients with psychotic tendencies. This fact must be emphasized since at present we are seeing a great many hyperthyroid patients whose disease is only partially controlled or with relapsing hyperthyroidism who can ill afford further systemic depletion. Complete control is not accomplished chiefly because of inadequate observation or understanding of antithyroid therapy on the part of the physician or the well recognized tendency of patients

to alter or discontinue therapy in the event that symptoms or signs appear that are unattributable to the medication that is being administered.

Other serious objections to maintenance treatment include such important factors as failure to bring about cure of the hyperthyroidism, persistence of goiter, inherent dangers in not removing adenomatous goiters, possible reactions to the medication, and possible development of serious histopathological change in the thyroid gland.

All these objections must be given careful consideration when maintenance management is under-

22 per cent.<sup>8</sup> With this knowledge added to other objections, including tracheal deviation and compression, it seems unwise to discard thyroidectomy in this type of goiter in which the results have been so completely satisfactory. The possibility of a reaction to the medication, although small, is real, and past experience has shown that there is no time during which one can feel entirely safe with their administration. Recent experimental work by Money and Rawson<sup>9</sup> on the prolonged use of thiouracil in rats has shown the development of cystadenomas in the thyroid gland, which appear to have malignant potentialities. Whether similar changes will occur in thyroid glands in human beings or whether administration of Lugol's solution

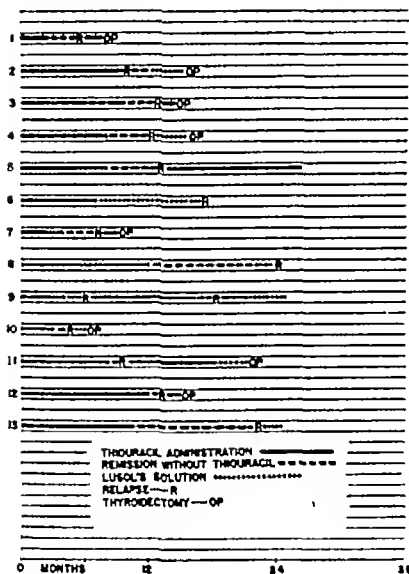


FIGURE 5. Relapse of Hyperthyroidism after Treatment with Thiouracil in Severe Hyperthyroidism with Substantial Thyroid Enlargement (Reproduced from Bartels<sup>8</sup> by Permission of the Publisher).

taken. Few patients are likely to choose prolonged treatment that in the end is not curative when a satisfactory surgical approach is available. The continued presence of the goiter, even though it is inactive, connotes potential trouble and indicates to the patient that he has not been cured of his disease. Over the years surgeons interested in thyroid disease have taught the advisability and urged the removal of adenomatous goiters, especially if single. Removal of such goiters seems necessary because of the possibility of malignant change, which some investigators have placed as high as

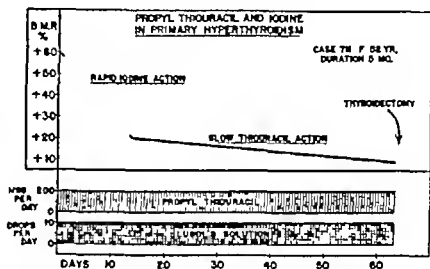


FIGURE 6. Simultaneous Administration of Propylthiouracil and Lugol's Solution Producing Rapid Initial Drop in the Basal Metabolic Rate Followed by a Slow Fall to Normal.

mitigates the danger of these tumor formations is not known.

#### ADJUNCT TO THYROIDECTOMY

Our chief experience with the antithyroid drugs has been in the field of preparing patients for thyroidectomy. It has been found that when treatment with these drugs is carefully managed, subtotal thyroidectomy can be carried out without risk, and hyperthyroid reactions during anesthesia and after operation, which in the past have caused great concern, are completely eliminated. Initially only severely hyperthyroid patients were treated preoperatively with these drugs, but since propylthiouracil has been available an increasing number of such patients are receiving the drugs. Patients with milder hyperthyroidism, however, are still prepared with Lugol's solution alone.

When these drugs are employed as a preoperative agent it is essential that they be used until full benefit is obtained, which is indicated by complete relief of all hyperthyroid signs and symptoms and return of the basal metabolic rate to nearly normal. Furthermore, it is advisable to maintain certain



patients at a normal metabolic level for a month or more before proceeding with thyroidectomy. These include patients in the older age group, those with long-standing hyperthyroidism, especially owing to adenomatous goiter, those who have suffered great visceral depletion, thyrocardiac patients in whom it is advisable to restore the heart to normal compensation and reserve and patients with related or unrelated psychoses.

Early in our experience, Lugol's solution was given for three weeks before operation to overcome the vascularity of the thyroid gland that occurs with thiouracil treatment when patients with primary hyperthyroidism are prepared for thyroidec-

tomies, and two days of treatment is required for each percentage of elevation of the basal metabolic rate.

In the last four years 830 patients have been prepared for thyroidectomy with antithyroid drugs, thiouracil being used in 381, thiobarbital in 28 and propylthiouracil in 421 patients. There was 1 death on the second postoperative day owing to coronary disease—an operative mortality of 0.12 per cent (Fig. 7) as compared with 1.49 per cent prior to the preoperative use of these drugs. Two-stage operations have been reduced from an average of 16 per cent to practically nil—only one such operation was done in 1946, and one so far in 1947.

Those who champion the medical treatment of hyperthyroidism condemn thyroidectomy as a useful procedure. We believe, as a result of our experience, that proper preparation of the hyperthyroid patient with antithyroid drugs followed by thyroidectomy offers the best chance of restoration to health in the shortest period of time with minimal risk. The objections to thyroidectomy (the incidence of tetany or unilateral vocal-cord paralysis should not be greater than 0.5 per cent) are usually surmountable. Of these two conditions, only tetany is admittedly an objectionable condition requiring careful and prolonged therapy. Myxedema, which occurs in 2 per cent of cases, is not greatly objectionable, since it can be easily and completely controlled by a daily dose of desiccated thyroid. Myxedema may actually be welcomed by those who fear a recurrence of hyperthyroidism. The recurrence rate after two years in those patients treated preoperatively with antithyroid drugs is 2 per cent, half these patients required reoperation for removal of thyroid remnants, and half obtained full control after a daily dose of Lugol's solution. Therefore, thyroidectomy after proper preoperative treatment resulted in cure in 95 per cent, with only tetany or recurrence representing a serious disadvantage.

#### SUMMARY

The new antithyroid drugs, if properly administered, will lower the basal metabolic rate of all patients with primary hyperthyroidism or adenomatous goiter with hyperthyroidism. All signs and symptoms of hyperthyroidism except prominence of the eyes subside, if present at the beginning of treatment.

Present information indicates that these drugs act on the thyroid gland by preventing the synthesis of stored iodide to an active protein-bound hormone.

The comparative effective daily doses of thiouracil and propylthiouracil are 600 mg and 200 mg, respectively.

The toxicity incidence of thiouracil is 9 per cent, and that of propylthiouracil 1.6 per cent. Therefore, propylthiouracil is the drug of choice, but since it may affect the white-cell elements its use is not without danger.

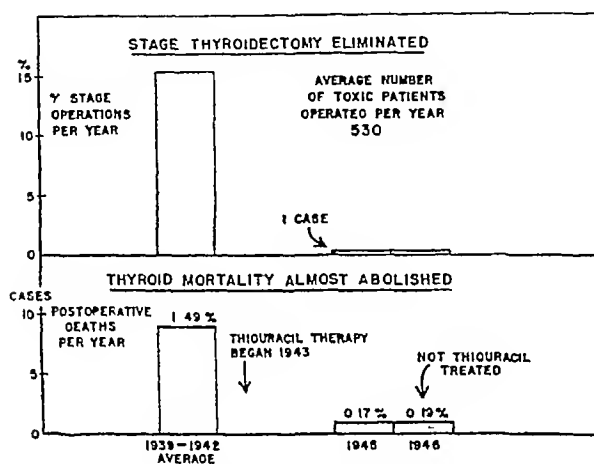


FIGURE 7 Comparison of the Percentage of Hemithyroidectomies Done before and since the Use of Antithyroid Drugs (Also, the Decrease in the Operative Mortality from 1.42 to 0.12 per cent is Shown)

tomy. Now patients receive propylthiouracil and iodine simultaneously from the beginning of treatment. With this new plan (Fig. 6), improvement starts promptly owing to the quick action of Lugol's solution, and through the action of propylthiouracil, improvement is sustained until full control of the hyperthyroidism is obtained. Iodine therapy, therefore, has two important functions: one of aiding in early clinical improvement, and the other of reducing the vascularity of the thyroid gland in preparation for easy thyroidectomy.

The use of Lugol's solution with propylthiouracil from the onset\* of therapy has delayed the ultimate recovery in that the average drop in the basal metabolic rate is now estimated as 1 per cent and 0.8 per cent as compared with 1.3 per cent and 1 per cent, respectively, in patients with hyperthyroidism of short duration and those with long-standing hyperthyroidism. The slowing effect of Lugol's solution, however, is not objectionable, since it is outweighed by the rapid clinical improvement. Patients with adenomatous goiter do not require

\*Further studies show that patients who have primary hyperthyroidism with large goiters should be treated by the old plan since response to therapy may be indefinitely delayed by the use of both Lugol's solution and propylthiouracil from the beginning of treatment.

Prolonged remission of hyperthyroidism after antithyroid treatment may occur in cases of mild hyperthyroidism with slight thyroid enlargement. In cases of severe hyperthyroidism with sizable goiters the incidence of prolonged remission is low.

Management therapy with antithyroid drugs is possible, but this type of treatment has some objections, including certain definite risks.

As preoperative adjuncts to thyroidectomy these new drugs have filled a great need and if properly used permit the elimination of operative reactions and mortality.

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## NEUROLOGIC DISTURBANCES WITH FOLIC ACID THERAPY\*

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THERE are numerous reports in the literature of the past two years on the excellent results obtained with folic acid in the treatment of pernicious anemia, sprue and nutritional macrocytic anemias. The observations presented below suggest some limitations of the therapeutic value of folic acid‡ and indicate that its use, in the present state of knowledge, for the treatment of pernicious anemia entails a definite risk.

### MATERIAL AND OBSERVATIONS

Fourteen cases of macrocytic anemia, 10 of pernicious anemia, 1 of tropical sprue, 2 of nontropical sprue, and 1 of macrocytic anemia associated with total gastrectomy were studied.

#### Pernicious Anemia

Cases 2, 3, 4, 7 and 10 occurred in patients with classic signs and symptoms of pernicious anemia who had initially shown excellent responses to the intramuscular use of refined liver extract. They had remained asymptomatic and without hematologic or neurologic relapse for several years on doses of 1 U.S.P. unit (injectable) a day given intramuscularly at intervals of four to six weeks. To determine the effect of folic acid, liver-extract therapy was stopped. The patients were then started on the folic acid regimens indicated in Table 1. As shown in the table, 3 patients (Cases 2, 3 and 4) had neurologic relapses with diminution in the vibratory sense

in each. Two (Cases 2 and 3) were asymptomatic when the diminution of the vibratory sense was first demonstrable. However, 1 patient (Case 4) also complained of the appearance of numbness and tingling of the hands and feet associated with a sense of weakness, although no gross increase in papillary atrophy developed, the same patient began to complain of "burning" of the tongue. These relapses occurred from six to twelve months after folic acid therapy was started.

Two patients (Cases 7 and 10) have not shown neurologic relapses after nine and four months of therapy on 5 and 10 mg. of folic acid a day, respectively.

The following cases of pernicious anemia are presented in more detail because of individual variations.

**CASE 1.** A 40-year-old woman was admitted to the hospital with the chief complaint of weakness. The family and past histories were noncontributory. The present illness had begun approximately 2 years previously with transient sore tongue, easy fatigability and slowly progressive weakness. The pertinent physical findings were pallor, slight icterus, retinal hemorrhages, papillary atrophy of the tongue, a positive bilateral Babinski sign and slight diminution of the vibratory sense in the left leg. A serologic test for syphilis was negative. The red-cell count was 730,000, with a mean corpuscular volume of 134 cu. microns and a mean corpuscular hemoglobin concentration of 29 per cent. There was no free hydrochloric acid in the gastric secretions after the administration of histamine. Many megaloblasts were present in the sternal marrow. After being on 25 mg. of folic acid orally per day for 8 days the patient complained of sudden inability to void urine. Cystometric studies showed a toleration of 900 cc. of water without a voiding response. When once initiated the voiding response was well maintained. There was no residual urine. This was interpreted as indicating a sensory lesion. A marked progression in the loss of vibratory and position senses was evident at that time. The patient was immediately started on intramuscular liver-extract therapy. Seventy-six days later she was not anemic and had no difficulty in voiding. She continued to have

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‡The folic acid employed in this work is synthetic pteroylglutamic acid and was supplied as Folivite through the courtesy of Dr. S. M. Hardy of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

slightly diminished vibratory sense over the left leg and a positive bilateral Babinski sign but was otherwise asymptomatic

**CASE 5** A 31-year-old Negress had been well maintained for several months on liver extract at the rate of 1 *USP* unit (injectable) a day given intramuscularly every 4 weeks. At the beginning of this study the patient was asymptomatic.

she was asymptomatic. There was no papillary atrophy of the tongue. Neurologic examination was negative. Examination of the blood showed a red-cell count of 4,750,000. The mean corpuscular volume was 89 cu microns, and the mean corpuscular hemoglobin concentration was 31 per cent. At the end of 7 months of therapy the patient complained of occasional sore tongue and numbness in the left leg. At the end of 10 months she complained of severe numbness and

TABLE 1 Data in 14 Cases Treated with Folic Acid

CASE No	AGE	RACE	SEX	DIAGNOSIS	RED CELL COUNT				MAXIMUM RETICULOCYTE COUNT	FOLIC ACID THERAPY		REMARKS
					INITIALLY	AFTER 2 WK.	ON LAST DAY	%		AMOUNT	ROUTE AND SCHEDULE	
1 (J H H 411311)	40	W	F	Pernicious anemia	1 26	—	1 54	8 4	25	Orally, daily for 8 days		Vibratory sense diminished during therapy, difficulty in voiding
2 (J H H 227321)	73	W	F	Pernicious anemia	4 97	—	—*	—	10	Orally, daily for 12 mo		By 12th mo diminution of vibratory sense demonstrable at both ankles
3 (J H H 240237)	42	W	F	Pernicious anemia	4 56	—	—*	—	10	Orally, daily for 11 mo		By 11th mo diminution of vibratory sense demonstrable at both ankles and both wrists
4 (J H H 139407)	47	N	F	Pernicious anemia	4 17	—	—*	—	20	Orally, daily for 6 mo		By 6th mo numbness and tingling of hands and feet with sense of weakness. Vibratory sense in left leg diminished, burning sensation of tongue
5 (J H H 365004)	31	N	F	Pernicious anemia	3 20	—	4 75	—	5	Orally, daily for 10 mo		By 10th mo vibratory sense at ankles, knees and iliac crests diminished. Sore tongue noted
6 (J H H 268067)	48	N	F	Pernicious anemia	1 41	2 85	4 20	15 4	30	Orally, daily for 27 days		By 8th mo numbness and tingling of hands and feet, unsteady gait, disappearance of abdominal reflexes and ankle jerks marked diminution in tactile sensation, plantar responses not elicitable, urgency and dribbling of urine. Relapse abrupt in onset and rapid in course.
7 (J H H 159654)	50	W	M	Pernicious anemia	4 66	—	—*	—	5	Orally, daily for 9 mo		After 9 mo no symptoms or signs of relapse
8 (J H H 377206)	56	W	M	Pernicious anemia	1 60	2 18	4 40	7 6	20	Orally, daily for 35 days		By 35th day numbness and tingling had appeared and progressed. Severe soreness of tongue associated with glossal petechiae
9 (J H H 372244)	74	W	F	Pernicious anemia	1 10	3 10	4 80	42 0	100	Intravenously, daily for 26 days		By 11th mo progression of loss of vibratory sense with numbness and tingling of hands and feet
10 (J H H 194679)	60	W	M	Pernicious anemia	5 45	—	—*	—	15	Orally, daily for 11 mo		After 4 mo no symptoms or signs of relapse
11 (J H H 391961)	70	W	F	Tropical sprue	2 64	3 60	3 70	9 2	45	Orally, daily for 20 days		After 20 days dramatic improvement, no neurologic disturbance
12 (J H H 286997)	65	W	M	Nontropical sprue	2 29	3 0	4 62	5 0	30	Orally, daily for 45 days		After 45 days moderate improvement, no neurologic disturbance
13 (J H H 130433)	43	W	M	Nontropical sprue	3 66	—	—*	1 2	100	Intravenously, daily for 5 wk		No definite improvement, no neurologic disturbance
14 (J H H 375636)	47	N	F	Pernicious anemia†	1 51	2 18	2 2	3 4	45	Orally, daily for 18 mo		
									600	Intravenously, daily for 14 days		Slight improvement with folic acid, slow but progressive improvement with liver extract
									300	Intravenously, daily for 2 days		

\*No significant change.

†This patient had undergone total gastrectomy

She was taken off liver-extract therapy for a period of 4 months. At the end of that time she noted easy fatigability. Physical examination revealed no unusual conditions. Examination of the blood showed that the red-cell count had fallen to 3,200,000, with a mean corpuscular volume of 112 cu microns and a mean corpuscular hemoglobin concentration of 31 per cent. The patient was started on 5 mg of folic acid orally a day. At the end of 5 months of therapy

tingling in the arms, hands, legs and feet. The ankle jerks were of high threshold, with brief and sluggish response. The vibratory sense was diminished over the ankles, knees and iliac crests. The hematocrit remained at 44 per cent.

**CASE 6** A 48-year-old Negress, who had been followed periodically for several years at the Johns Hopkins Hospital with the complaint of weakness, had responded well

to liver extract intramuscularly at first but after 3 years of infrequent attendance in the Outpatient Department she reappeared complaining of general weakness with numbness of the hands and feet. Physical examination showed marked pallor, slight papillary atrophy of the tongue and diminution of vibratory sense over the legs. A serologic test for syphilis was negative. Examination of the blood revealed a red-cell count of 1,410,000 with a mean corpuscular volume of 116 cu microns and a mean corpuscular hemoglobin concentration of 34 per cent. Gastric secretion disclosed no free hydrochloric acid after the administration of histamine. The patient's blood responded dramatically to daily oral doses of 30 mg of folic acid (Table 1). On the 28th day the daily dose was lowered to 10 mg. Six months after the beginning of treatment she was asymptomatic. Three months later however she returned complaining of abrupt onset of numbness and tingling in the hands and feet. She noted unsteadiness of gait and had some urgency and dribbling of urine. The tone of the adductor femoris muscles was increased. The abdominal reflexes and ankle jerks had disappeared. No plantar responses were elicited. Tactile sensation and appreciation of pinprick had markedly diminished over the legs.

CASE 8. A 56-year-old machinist was admitted to the hospital with the complaint of a sore tongue and "feeling run down." The family and past histories were noncontributory. The present illness had begun 7 months prior to admission with anorexia, sore tongue and weakness. Physical examination showed pallor, injection and atrophy of the glossal papillae and normal neurologic signs. A serologic test for syphilis was negative. Examination of the blood disclosed a red-cell count of 1,600,000 with a mean corpuscular volume of 137 cu microns and a mean corpuscular hemoglobin concentration of 31 per cent. There was no free hydrochloric acid in the gastric secretion after the administration of histamine. The sternal marrow showed numerous megaloblasts. The patient's blood revealed a good response to 20 mg of folic acid a day orally (Table 1). However after 35 days numbness and tingling of the hands and feet appeared and progressed in severity. The soreness of the tongue became extremely annoying. Occasionally the glossal surface showed tiny petechiae, and the papillae remained injected. The patient was started on liver extract intramuscularly. The soreness of the tongue, as well as the numbness and tingling of the hands and feet, disappeared by the end of 1 week.

CASE 9. A 74-year-old housekeeper had first been admitted to the hospital in 1927 with pernicious anemia. For 1 year prior to the last admission in 1945 the patient had received no treatment. For several months she had noted increasing fatigability, dyspnea, slight ankle edema, a sore tongue and numbness and tingling of the hands and feet. Physical examination showed marked pallor, marked papillary atrophy of the tongue and diminution of the vibratory sense over both legs. A serologic test for syphilis was negative. Examination of the blood disclosed a red-cell count of 1,110,000 with a mean corpuscular volume of 135 cu microns and a mean corpuscular hemoglobin concentration of 32 per cent. An occasional megaloblast was present in the peripheral blood. The patient was given intravenously 100 mg of folic acid a day, prepared according to the technique described by Darby et al.<sup>1</sup> By the end of the 1st week she felt much stronger. On the 6th day of therapy a reticulocyte peak of 42 per cent was attained (Table 1). On the 26th day the patient was changed to daily oral doses of 15 mg of folic acid. During the 10th month of such therapy numbness and tingling of the hands and feet recurred. The vibratory sense had disappeared below the costal margin and was diminished elsewhere.

## Sprue

CASE 11. A 70-year-old Porto Rican woman was admitted with the chief complaints of weakness, dizziness, vomiting and diarrhea. The patient's mother and sister had had a similar condition. The past history was noncontributory. Approximately 2½ years before admission loose, foul smelling numerous bowel movements had begun. Weight loss and sore tongue were noted. Weakness became extreme. She was given "liver injections" by a physician and improved markedly. A few months prior to admission she neglected further therapy and relapsed. Physical examina-

tion showed emaciation, pallor, injected and atrophic glossal papillae and slight generalized abdominal tenderness. Neurologic examination was negative. A serologic test for syphilis was negative. Examination of the blood revealed a red cell count of 2,640,000 with a mean corpuscular volume of 121 cu microns and a mean corpuscular hemoglobin concentration of 33 per cent. The sternal marrow showed 7 per cent megaloblasts. The stools which were pale, unformed, foul smelling and copious contained no occult blood and showed no pathogenic ova or parasites. The oral glucose tolerance and vitamin A absorption curves were flat.\* X ray studies of the gastrointestinal tract disclosed distortion of the mucosal pattern and pooling of the barium. The patient was placed on daily doses of 45 mg of folic acid orally. By the 8th day the stools were much less frequent and were well formed. A reticulocyte peak of 92 per cent was attained on the 5th day of therapy. She became quite jovial and felt much stronger. Kymographic tracings of intestinal motility before treatment and 12 days after treatment showed changes indicating less frequent and less marked peristaltic waves. A glucose tolerance test on the 17th day was normal. During the 3rd week of treatment the vitamin A absorption curve following the oral administration of 200,000 units remained quite flat, although the fasting serum vitamin A level had risen from 82 to 140 microgm per 100 cc. during therapy. On the 20th day of therapy the patient was started on liver extract intramuscularly since it was thought that she might neglect subsequent medical supervision and direction. She had developed no neurologic disturbances during folic acid therapy.

CASE 12. A 65-year-old laborer with known nontropical sprue of 4 years' duration had responded well to the intramuscular use of liver extract. After 9 months of withdrawal of liver-extract therapy the patient was admitted with the chief complaints of recurrent episodes of diarrhea, weakness and numbness and tingling of the hands and feet. Physical examination showed evidence of recent weight loss, pallor and glossal papillary atrophy, with normal neurologic signs. A serologic test for syphilis was negative. Examination of the blood disclosed a red-cell count of 2,290,000 with a mean corpuscular volume of 125 cu microns and a mean corpuscular hemoglobin concentration of 31 per cent. The two or three daily stools were well formed and had been for several days despite lack of medical therapy. The oral glucose tolerance curve was flat, but the intravenous curve was normal. Folic acid was administered in doses of 30 mg a day orally. On the 6th day of therapy a reticulocyte peak of 5 per cent was attained (Table 1). On the 21st day of therapy the vitamin A absorption curve remained flat (ranging from 38 to 54 microgm per 100 cc. in the fasting and 3 hour serum specimens) on the following day the glucose tolerance curve was normal. X ray studies of the gastrointestinal tract 3 weeks after the institution of therapy continued to show alterations compatible with the clinical diagnosis of sprue. There were no episodes of diarrhea during a 45-day observation period. The patient gained 18 pounds in weight during that time, and the red-cell count rose to 4,620,000 with a mean corpuscular volume of 97 cu microns. No neurologic disturbances developed during folic acid therapy.

CASE 13. A 50-year-old man was followed medically over a period of 10 years with nontropical sprue. The family and past histories were noncontributory. During observation the patient had bulky frothy, yellow foul-smelling stools from four to seven times or more daily despite liver-extract given intramuscularly every 4 weeks at the rate of 1 U.S.P. unit (injectable) per day. Physical examination showed evidence of weight loss, pallor, no glossal papillary atrophy and a protuberant soft abdomen, with normal neurologic signs. A serologic test for syphilis was negative. Examination of the blood revealed a red-cell count of 3,660,000 with a mean corpuscular volume of 109 cu microns and a mean corpuscular hemoglobin concentration of 31 per cent. The gastric secretion contained free acid. Folic acid in daily intravenous doses of 100 mg was administered for 6 weeks. The bowel movements remained profuse, bulky and unformed. The oral glucose tolerance curve remained flat and administration of vitamin A orally in an amount of 200,000 units caused a level of only 25 microgm per 100 cc. at the

\* Vitamin A determinations were made by Dr. H. W. Josephs.

end of 3 hours. X-ray studies of the gastrointestinal tract continued to show hypermotility and changes compatible with the diagnosis of sprue. On 45 mg of folic acid orally daily for 18 months the stools remained unformed and foul smelling and increased in number. The stool fat content remained high (42.5 per cent of the dry weight). The hematocrit did not rise. No abnormal neurologic signs or symptoms appeared.

### *Post-Gastrectomy Macrocytic Anemia*

**CASE 14** A 47-year-old Negress was admitted to the hospital with the chief complaint of inability to walk. The family history was noncontributory. The past history was of interest in that, 7 years prior to admission, the patient had been seen at another hospital complaining of abdominal cramps, anorexia and a 25-pound weight loss within a 6-month period. X-ray studies were interpreted as showing a gastric tumor mass. A total gastrectomy was performed. Microscopical sections of the gastric wall were subsequently studied by Dr. Arnold R. Rich and showed nonspecific lymphocytic infiltration. The patient remained asymptomatic and led a vigorous life until the present illness. Three months before admission the patient noted a rapid onset of numbness and tingling of the legs, associated with progressive inability to walk that became so severe 2 months later that she was confined to bed. There had been a 30-pound weight loss. Physical examination revealed evidence of recent weight loss, marked pallor and moderate papillary atrophy of the tongue. The tendon reflexes of the quadriceps femoris and semitendinosus were of very low threshold and showed brisk response. There was increased tone in the adductors of the legs and contractures of the gastrocnemius-soleus muscles. There was transient, partially sustained clonus on dorsiflexion of the left ankle. The Babinski signs were negative. The vibratory sense was absent below the iliac crests. Muscle strength was good. A serologic test for syphilis was positive. Examination of the blood revealed a red-cell count of 1,830,000, with a mean corpuscular volume of 128 cu microns and a mean corpuscular hemoglobin concentration of 30 per cent. The sternal marrow showed 19.5 per cent megaloblasts. Direct visualization at the lower end of the esophagus demonstrated an esophagojejunal anastomosis and no gastric mucosa. The patient was given 300 mg of folic acid intravenously daily for 2 days and 600 mg intravenously daily for 14 days. The neurologic status was so serious that progression or improvement in such a short time could not be evaluated accurately. The red-cell count rose 600,000, and the hemoglobin rose 2 gm per 100 cc in 16 days. The reticulocyte count reached a peak of 3.2 per cent on the 8th day of therapy. On the 17th day folic acid was stopped and liver extract was given intramuscularly (10 USP units of crude extract and 15 USP units of refined extract) daily for several days, followed by an average daily dose of 1.5 USP units (injectable) of refined liver extract given every 2 to 4 weeks. There was no second reticulocyte peak. After 6 months the patient was able to walk easily without a cane. She had no numbness or tingling. The red-cell count was 5,200,000 6 months after the beginning of liver-extract treatment.

### DISCUSSION

In the 10 cases of pernicious anemia treated with folic acid the patients who had anemia at the beginning of treatment showed very good hematologic responses. There was no hematologic relapse. Five patients had been asymptomatic while on liver-extract therapy for several years. However, 8 patients, while taking folic acid, showed neurologic disturbances of varying severity within periods ranging from eight days to twelve months. Two patients had difficulty with voiding of urine, 1 showing by cystometric study alterations suggesting a sensory lesion. Diminution in the vibratory sense and numbness and tingling in the hands and feet were the most frequent developments. One patient showed signs suggesting extensive damage to the reticulospinal

tracts. Two patients, while still asymptomatic, gave evidence of progressive diminution of the vibratory sense in the lower extremity. The onset of signs and symptoms in 2 cases was abrupt and severe. Usually, the neurologic changes appeared clinically to be most marked in the sensory as contrasted to the motor modality. Three patients had either progression or return of soreness and burning of the tongue. In 1 case this was associated with gross changes consisting of papillary injection, atrophy and petechial hemorrhages. This patient responded within a week to liver extract given intramuscularly, at the end of that time there was no soreness and no glossal petechiae.

One patient with tropical sprue showed excellent clinical and hematologic response to folic acid therapy, but of 2 patients with nontropical sprue only 1 had a remission. The other, who had not previously responded to liver extract, showed no change in the blood either on parenteral or oral dosage and no marked change clinically. No neurologic disturbances developed in the cases of sprue during folic acid therapy.

A patient with total gastrectomy of seven years' duration, associated with macrocytic anemia, severe neurologic changes and weight loss, did not show a marked reticulocytosis or clinical improvement over a sixteen-day period of intensive folic acid therapy parenterally. There was a definite though small rise in the red-cell count and hemoglobin level. Although subsequent liver extract did not cause any rapid changes there was gradual and progressive improvement over a period of several months both hematologically and neurologically.

The high incidence of pathologic neurologic signs and symptoms developing among patients with pernicious anemia who previously had been adequately controlled with liver extract indicates the inadequacy of folic acid therapy for this aspect of the disease. That these disturbances did not follow doses of folic acid that were simply too small is indicated by other observations. Spies et al.<sup>2</sup> have stated that increasing dosages to amounts of 500 mg a day have not ameliorated the progression of neurologic lesions in some cases. The abruptness and severity of neurologic relapse in an occasional case suggest the possibility of an actual deleterious effect of folic acid. In a series of 21 cases of pernicious anemia treated by Spies et al.<sup>2</sup> with doses of folic acid varying from 70 to 105 mg a week, paresthesias and unsteady gait developed in 4. The dosage was then increased to 50 and even 500 mg a day for ten to forty days without subjective or objective neurologic improvement. Nine other patients with subacute combined degeneration were then treated with folic acid. Two showed questionable improvement, whereas the remainder either became worse or did not improve. One patient revealed detectable progressive neurologic changes

after only twenty-two days of folic acid in daily oral doses of 10 mg

Hall and Watkins<sup>3</sup> have reported 14 cases of pernicious anemia in relapse treated with folic acid. Of 10 patients with paresthesias of the extremities 8 improved. However, improvement was only temporary in 4, in whom paresthesias returned two to four months after the beginning of therapy. Two patients who had not had paresthesias prior to folic acid therapy developed them five months after the institution of treatment. Castle and Berk<sup>4</sup> have observed a neurologic relapse in 1 of 10 cases of pernicious anemia treated with folic acid. The less frequent incidence in their series may have resulted from the mode of administration. Their patients were given 75 mg of folic acid intramuscularly at weekly intervals. Daily treatment was not given. Heinle and Welch<sup>5</sup> have observed an "explosive" and rapidly progressive neurologic relapse in a patient with pernicious anemia receiving folic acid therapy. Meyer<sup>6</sup> noted the development and progression of neurologic symptoms in 3 patients with pernicious anemia receiving folic acid in daily doses of 15 to 50 mg, orally, or 20 mg intramuscularly.

The high incidence of glossitis during the treatment of patients with pernicious anemia is another symbol of the inadequacy of folic acid in their therapy. One patient's main complaint was severe glossal pain. Papillary petechiae developed during treatment. Although folic acid did not improve the condition, liver extract caused marked improvement in the discomfort and the petechiae disappeared within a week. Hall and Watkins<sup>3</sup> have reported that of 7 patients with pernicious anemia sustained improvement of the glossitis occurred in only 3.

The excellent response of tropical sprue to folic acid treatment seems well established.<sup>7-9</sup> However, in a case of nontropical sprue reported above no convincing improvement occurred with either folic acid or liver-extract therapy. The response of the other patient is difficult to evaluate, since he was in partial clinical remission when therapy was begun. He had previously responded well to liver-extract treatment. Although so few observations warrant no definite conclusions, the differences in thera-

peutic effects in these 3 cases suggest that there are fundamental variants in the pathogenesis of sprue. Neurologic disturbances did not appear in any case of sprue during folic acid therapy.

#### SUMMARY

The development or recurrence of neurologic disturbances occurred in 8 of 10 cases of pernicious anemia treated with folic acid. No hematologic relapse was observed.

The development or recurrence of neurologic disturbances was occasionally abrupt and severe, as well as rapid in course. The time of appearance could not be predicted.

In 3 of 10 cases of pernicious anemia glossitis either occurred during or did not respond to folic acid therapy.

One patient with tropical sprue responded dramatically. One patient with nontropical sprue responded very well, whereas another did not show any convincing improvement on folic acid or liver-extract therapy. Neurologic disturbances did not develop in the cases of sprue during folic acid therapy.

There was a slow effect of folic acid and liver extract in a patient with macrocytic anemia following total gastrectomy.

The observations presented indicate that the use of folic acid in the present state of knowledge entails a definite risk of injury to the nervous system in pernicious anemia.

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## LIPEMIA RETINALIS\*

## Report of a Case

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**L**IPEMIA retinalis is a rare manifestation of the hyperlipemia that is commonly associated with diabetic acidosis. Since the original description by Heyl<sup>1</sup> in 1880, a total of 62 cases have been reported in diabetic and 6 in nondiabetic patients. The rarity of retinal lipemia is indicated by the experience of Joslin and his associates,<sup>2</sup> who discovered only 9 cases among 29,000 patients with glycosuria in a period of forty-eight years. However, the report of 7 patients with lipemia retinalis among 108 patients treated for diabetic acidosis at the Mayo Clinic<sup>3</sup> suggests that the condition is more frequent than was formerly believed.

The funduscopic picture of retinal lipemia is striking and pathognomonic. The vessels are flat, wide, ribbon-like and faint salmon to cream in color, with decreased or absent arteriolar reflex and with little or no distinction between arterioles and veins. The earliest changes are found at the periphery of the retina, advancing toward the disk during progression and receding with improvement. The changes, which may be transient, lasting only one or two days, usually do not disappear for a week, and may persist for even three weeks. Vision generally remains normal, despite the appearance of the retinal vessels. Three fourths of the reported cases have occurred among males and the majority of patients have been children or young adults, although the condition has been observed at the age of sixty-four years.<sup>4</sup>

The following case occurred in the youngest diabetic patient with lipemia retinalis on record.

## CASE REPORT

A 4½-year-old girl was admitted to the hospital because of a 7-week history of increasing lassitude, polyphagia, polyuria, polydipsia and weight loss, culminating in drowsiness and in the discovery of sugar and acetone in the urine 12 hours before entry. Prior to the onset of this illness, the child had been of normal height and weight for her age. There was no family history of diabetes, and the past history was not relevant.

Physical examination revealed a thin, apathetic child who neither spoke nor responded to painful stimuli. She weighed 31½ pounds. There were no skin lesions. The pupils were equal and active, and the lenses clear. The fundi, which were pale, contained striking cream-colored ribbon-like vessels, which could not be differentiated into arterioles and veins. The disks were normal. The ears, nose and throat were normal except for a strong odor of acetone on the

breath, dry mucous membranes and enlarged tonsils. There was no cervical adenopathy. The heart and lungs were normal. A firm liver edge could be felt one fingerbreadth below the right costal margin, but the abdomen was otherwise normal. Neurologic examination revealed only diminished deep tendon reflexes.

The temperature was 98.6°F by rectum, the respirations 25, and the pulse 120, the blood pressure was 110/75.

Urinalysis disclosed a +++ test for glucose and acetone, a ++ test for albuminuria and occasional leukocytes and epithelial cells in the sediment. Examination of the blood revealed a red-cell count of 4,150,000 and a white-cell count of 13,200, the smear was normal. When venous blood was placed in an oxalate bottle, the cells were noted to settle rapidly, leaving a creamy white supernatant plasma. Subsequent analysis disclosed a blood sugar of 256 mg and a nonprotein nitrogen of 21 mg per 100 cc and a carbon dioxide combining power of 19 vol per cent.

Immediately after entry, an intravenous infusion of physiologic saline solution was begun, and regular insulin was given subcutaneously at hourly intervals. By the end of the first 24 hours, the patient had received 300 units of insulin and 2900 cc. of saline solution of which 1300 cc. had also contained 5 per cent glucose. At that time the child was alert and responsive. The blood sugar was 85 mg per 100 cc., the carbon dioxide combining power was 27 vol per cent, and the urine was free of sugar and acetone. The blood cholesterol, which had not previously been determined, was 1010 mg per 100 cc. The retinal vessels were slightly pinker but still paler than normal.

In the course of the following week, the diet was gradually increased, and the insulin dosage adjusted. On the 7th hospital day, the fundi were completely normal. On the 14th day, the blood cholesterol was 313 mg per 100 cc. The liver was no longer palpable. X-ray examination of the skull and chest, a tuberculin test and urinalyses were all negative. The patient gradually gained weight and was discharged on the 23rd hospital day, when the fasting blood sugar was 94 mg and the cholesterol 321 mg per 100 cc. The 24-hour urinary glucose excretion was 14.5 gm on a diet of 165 gm of carbohydrate, 70 gm of protein and 70 gm of fat, 12 units of protamine-zinc insulin and 12 units of regular insulin injected separately constituted the daily morning insulin dosage.

## DISCUSSION

Although quantitative fat determinations were not carried out, the cholesterol level of 1010 mg per 100 cc., the creamy appearance of the plasma and the pathognomonic retinal picture established the diagnosis of lipemia retinalis in this case—the 63rd case and the youngest diabetic patient with this condition to be reported.

The rarity of such cases and the transitory nature of the retinal changes make it difficult to carry out experimental procedures that might result in an understanding of the pathogenesis of this condition. It is therefore worth while to summarize and correlate some of the observations that have already appeared in the literature.

Although lipemia retinalis has never been reported in the absence of hyperlipemia, a rise in blood fats does not in itself produce the condition. Uncon-

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trolled diabetes and diabetic acidosis are frequently associated with hyperlipemia, but since 1880 only 62 cases of lipemia retinalis have been reported in diabetic patients. Furthermore, retinal lipemia has not been reported in conjunction with any of the numerous other conditions usually associated with hyperlipemia, such as starvation, asphyxia, phosphorus poisoning, pneumonia, nephritis, peritonitis and myxedema.

The conclusion that lipemia retinalis appears when blood lipids exceed 35 per cent and disappears when they decrease below 25 per cent<sup>4</sup> is not borne out by other observations. Persistence of retinal lipemia has been noted at a blood lipid level of 142 per cent,<sup>6</sup> and disappearance of the retinal changes has been reported during a rise in blood lipids from 9.15 to 10.8 per cent<sup>7</sup> and during a decrease from 21.7 to 16.3 per cent.<sup>8</sup>

Neither an elevated blood sugar nor the presence of diabetic acidosis is a necessary condition for the development of lipemia retinalis. A few cases of retinal lipemia have been reported in nondiabetic patients<sup>9-14</sup> in whom there was no evidence of acidosis. At least 2 of the diabetic patients with lipemia retinalis did not have simultaneous acidosis.<sup>15, 16</sup>

Attention has been called<sup>14</sup> to the observations of Boyd,<sup>17</sup> who found that milky serums sometimes contain normal amounts of fat whereas clear serums sometimes contain rather large amounts of fat. Visibility of the blood fats can be correlated with a relative decrease of phospholipids, so far as the total amount of natural fat, fatty acids, cholesterol and cholesterol esters is concerned.<sup>17</sup> Boyd concluded that phospholipids tend to maintain the other fat fractions in a supersaturated state in serum, when the phospholipid content of serum diminishes, lipids come out of solution as chylomicrons forming a milky emulsion. Such fat droplets have been demonstrated in lipemia retinalis in blood smears,<sup>18</sup> in capillary loops by the Lombard technique,<sup>7</sup> in muscle biopsy for frozen section and Sudan III stain<sup>19</sup> and in autopsy material.<sup>20</sup> The size of some of these droplets has been estimated as varying from that of a red cell to approximately 20 microns in diameter.<sup>7</sup> In normal serum, however, chylomicrons vary from 35 millimicrons to 1 micron in diameter.<sup>21</sup>

A relative decrease in phospholipids has indeed been observed in diabetic acidosis, in which Man and Peters<sup>22</sup> found that serum fatty acids rose much more than either the serum cholesterol or the phospholipids. In 2 cases of lipemia retinalis Marble and Smith<sup>23</sup> observed that the greatest increase in the blood fats had occurred in the fatty acid fraction, the next greatest in the cholesterol, and the least in the phospholipid fraction. A decrease in organic acid soluble phosphorus of the blood cells occurs with diabetic acidosis,<sup>24</sup> indicating a depletion of labile phosphorus reserves.<sup>25</sup> Significantly, although the blood chloride, sugar and carbon

dioxide combining power promptly return to normal and phosphaturia promptly ceases with adequate treatment, the organic acid soluble phosphorus of the blood cells does not become normal for a week, at which time phosphaturia reappears.<sup>26</sup>

It seems probable, therefore, that depletion of phosphate reserves plays an important role in the pathogenesis of lipemia retinalis. A review of the literature reveals, in every completely reported case, a long preliminary period of uncontrolled diabetes, frequently with much weight loss and malnutrition. Although specific details are not presented in most cases of lipemia retinalis in nondiabetic patients, there is some reason to believe that the periodic vomiting, marasmus, alcoholic gastritis or hepatosplenomegaly variously reported in these cases had some bearing on the nutrition of the patients.

### SUMMARY AND CONCLUSIONS

The 63rd and youngest patient with diabetic lipemia retinalis is reported. Lipemia retinalis is a retinal manifestation of hyperlipemia with a changed state of blood lipids in the direction of formation of larger than normal chylomicrons. Whatever the cause of the hyperlipemia, there is some evidence that the changed state of the blood fat results from depletion of phospholipids. This in turn may be due to a long period of malnutrition with, in diabetes mellitus, a specific loss of phosphates in the urine.

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## MEDICAL PROGRESS

## THE TOXEMIAS OF PREGNANCY

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**T**HIS review of the toxemias of pregnancy considers the four syndromes involving primarily hypertension with or without albumin in the urine. The first two are essential hypertension and renal disease, they may or may not be influenced by pregnancy. Secondly, pre-eclamptic toxemia and eclampsia are discussed. These conditions are the result of the pregnancy itself. It should be stated in the beginning that clinical diagnosis and classification are frequently difficult and often impossible. If a patient is first seen after she has become pregnant, the presence of hypertension or albuminuria or both offers a very confused picture. There are many leads suggesting the fundamental disease, which may or may not be present, but, in many cases, the final diagnosis cannot be confirmed until months after the patient has been delivered. Even then, there may be doubt regarding the actual condition involved.

It is also extremely important to realize that in all cases in which there is basic renal or vascular disease, true toxemia of pregnancy may be superimposed on the original condition. In fact, any pregnant woman who has had renal or vascular disease previous to pregnancy has a much greater chance of developing true toxemia than one with a healthy renal vascular system. For instance, a woman with chronic nephritis may become extremely ill in pregnancy from the chronic nephritis, but she may become more acutely and rapidly ill from the development of a superimposed pre-eclamptic toxemia. Frequently, it is extremely difficult to recognize when a previous renal vascular disease develops into pre-eclamptic toxemia. Fortunately the treatment is in a large degree essentially the same, but the prognosis and the speed with which dangerous symptoms develop vary in the different conditions. A woman with chronic nephritis can carry a much greater hypertension with reasonable safety than one with a true pre-eclamptic toxemia. A patient with essential hypertension may go through pregnancy uneventfully with a hypertension that in a pre-eclamptic might suddenly develop into eclampsia. Therefore, the best clinical judgment and all available laboratory facilities must be used to distinguish between the different entities. Dexter and Weiss<sup>1</sup> emphasize the importance of the distinction in the following statement: "Organs

weakened by pre-existing hypertensive disease are more susceptible to the strain imposed upon them by toxemia than are organs previously healthy, there being a greater tendency to cardiac decompensation, renal insufficiency, and more severe retinal lesions."

## ESSENTIAL HYPERTENSION

Essential hypertension in pregnancy is a hypertension that existed previous to pregnancy. There are cases in which, although no hypertension has been recorded before pregnancy, the disease or tendency exists and shows up early in pregnancy. It is reasonable to state that any hypertension developing in the first half of pregnancy is not pre-eclamptic toxemia. Without any signs of permanent kidney damage, this rise in blood pressure is presumably due to essential hypertension. If a patient develops a blood pressure of 140 systolic, 90 diastolic, before or during the first half of pregnancy, without signs of kidney damage, the case must be classed as essential hypertension. In this hypertension the systolic pressure frequently rises to 180. In mild cases there is little else to show, and the patient feels well. There is usually no albumin in the urine. These patients will generally do well. They must be watched more carefully than the normal patient, and they must be more careful of their diet and activities, owing to the greater danger of developing toxemia.

The etiology of essential hypertension is unknown, as is that of pre-eclamptic toxemia. The similarity of the two conditions is marked, since in both cases, the primary hypertension is due to spasm of the arterioles. In essential hypertension the long-continued progress of the disease causes hypertrophy of the arteriolar muscle and finally degeneration of that muscle with fibrous displacement. The duration of pre-eclamptic toxemia is sufficiently limited so that this final permanent damage to the arterioles does not take place. However, if the toxemia is allowed to continue too long, permanent damage to the arterioles takes place. In the benign type of hypertension, permanent kidney damage is a late complication. In the malignant type, renal insufficiency develops early, and this is the chief danger. There is probably a marked hereditary tendency in essential hypertension. Certain people have a marked constitutional abnormality, which may lead to the

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development of hypertension. The cold pressor test is of interest, in that the great majority of essential hypertensive patients give positive reactions. Also, a large number of otherwise normal people who react to this test will eventually develop hypertension.

The work of Grollman<sup>2</sup> in essential hypertension suggests a relation to pre-eclamptic toxemia. He states that the kidney — by some humoral, if not by an incretory, mechanism — may be concerned in the pathogenesis of hypertensive cardiovascular disease as commonly observed in man, and as produced with ease in the experimental animal. The fact that hypertension follows manipulations of the kidney, as well as the high incidence of hypertension observed in the human being with kidney disease, leaves little doubt that the experimental disease, as well as many cases of clinical hypertension, is secondary to dysfunction of the kidney.

According to Grollman<sup>2</sup> the removal of the injured kidney, either in man or in animals, does not lower the blood pressure. If one kidney is injured and the other is removed, there is an immediate rise in the pressure. In contrast to much previous work, he believes that the normal kidney produces an incretory substance that regulates the normal blood pressure, and that the removal of normal kidney tissue, or damage to it, removes this control over blood pressure and thus results in hypertension.

The work of Smithwick<sup>3</sup> in lumbodorsal sympathectomy throws an interesting light on the relation of essential hypertension to pre-eclamptic toxemia. The marked lowering of hypertension following this operation frequently allows patients to proceed uneventfully through pregnancy. These patients, with the hypertension previous to operation, would be serious risks for pregnancy. One patient in particular, who with a previous pregnancy developed severe cerebral and visual disturbances, had to have the pregnancy terminated at seven months. After a sympathectomy, she went uneventfully through a normal full-term pregnancy. In spite of this operation some of these patients develop pre-eclamptic toxemia. In a series of 13 cases reported by Newell and Smithwick,<sup>4</sup> 3 patients developed definite signs of pre-eclamptic toxemia, 1 had a premature separation of the placenta, and in 1, labor had to be induced before term.

The prognosis of essential hypertension of the benign type in pregnancy is good. The majority of these patients have an uneventful pregnancy. The incidence of pre-eclamptic toxemia is higher in them than in normal women, and they should be watched more carefully. Particularly, they should have sufficient rest, a careful diet and a minimum weight gain. Any increase in hypertension, or the appearance of albumin in the urine, indicates the probability of the development of pre-eclamptic toxemia. Dexter and Weiss<sup>1</sup> believe that women with pre-pregnant hypertension (essential hypertension) pass

through pregnancy without damage if they do not develop pre-eclamptic toxemia. They consider an added risk to the fetus to exist in these cases. Sharkey and Hess<sup>5</sup> state that pregnancy causes no significant change in essential hypertension. They do not regard the hypertension as having any effect on the infant. In their own series, these patients did as well as the normal women.

In a series of 301 pregnant patients, Chesley, Annitto and Jarvis<sup>6</sup> report 218 cases classifiable as hypertensive toxemia. The outstanding hazard of pregnancy is the superimposition of toxemia, which occurred in about 30 per cent. The incidence of eclampsia in these hypertensive patients was ten times that in all patients, whereas the incidence of pre-eclampsia increased seven times. The gross fetal mortality was 34 per cent. The majority of hypertensive women apparently are not jeopardized by pregnancy; two thirds of these patients escaped superimposed toxemia. In patients who did not have toxemia, 30 per cent had greater hypertension at follow-up study than when originally observed. The authors conclude that repeated pregnancies are not harmful to the hypertensive woman. The pregnancy itself is hazardous should toxemia occur. If the toxemia causes damage, the prompt interruption of a hypertensive pregnancy, at the first sign of developing toxemia, should benefit the patient.

Essential hypertension of the malignant type is a more serious disease. Without pregnancy, the prognosis of these patients is poor. The added strain of pregnancy is apt to precipitate serious complications. Pregnancy should be definitely avoided in such cases.

#### RENAL DISEASE

The differentiation of the various forms of kidney disease is somewhat of an academic problem. The separate types — glomerular, arteriosclerotic, nephritic and pyelonephritic — offer great difficulty in differential diagnosis. It is vital that the clinician recognize permanent kidney disease. All types of kidney disease are alike, in that they respond poorly to pregnancy. Any damaged kidney has a lowered reserve. The additional load of pregnancy may be too much for this lack of reserve. Pregnancy may cause renal failure. Patients with damaged kidneys may develop a superimposed pre-eclamptic toxemia. The incidence of toxemia in these patients is much higher than that in normal persons. It is often extremely difficult to judge when a nephritis may show renal failure in pregnancy, but the addition of toxemia will make the condition more acute and rapid in progress. It is also essential to realize that patients may have renal disease from childhood infections, or other causes, of which they are entirely unaware. Often, it is the first pregnancy that brings the kidney disease to light. A negative past history obtained from a patient does not rule out the possibility of renal damage.

The symptoms of renal disease appear early in pregnancy. The milder forms may not appear until later. It is the mild forms that are most frequently confused with pre-eclampsic toxemia. A patient who appears during the first months of pregnancy with hypertension, albuminuria and edema should be studied for the presence of nephritis. The systolic blood pressure is variable, sometimes being over 200, usually it is lower. Extremely high blood pressures with no cerebral symptoms are characteristic of chronic nephritis rather than pre-eclampsia. The urine will show albumin, and frequently casts and red cells, in contrast to pre-eclampsia. The blood pressure does not fall immediately after delivery as in pre-eclampsia but continues for months and often permanently. The albumin may persist after delivery. Nitrogen retention may be present in the severe cases as shown by a high blood nonprotein nitrogen. In pre-eclampsia there is no nitrogen retention. According to Stander<sup>7</sup> a high nonprotein nitrogen is pathognomonic of kidney disease. This is not found in pre-eclampsia unless eclampsia develops. According to Stander a study of the renal-function tests is essential. In pre-eclampsia the kidney function is normal, whereas in kidney disease a decreased function is often found. Stander recommends the fifteen-minute phenol-sulfonephthalein, the urea clearance and the dilution and concentration tests. He believes that the dilution and concentration test is the most sensitive to slight degrees of kidney damage. Examination of the eye grounds frequently shows the presence of retinal hemorrhage and albuminuric retinitis, which is absent in pre-eclampsia.

The prognosis of renal disease in pregnancy is poor. Stander gives the average maternal mortality occurring within ten years, after the disease has been recognized, as 40 per cent. Each pregnancy increases the kidney damage and undoubtedly shortens the life of the patient. The prognosis for the babies is extremely poor. DeLee<sup>8</sup> gives the fetal mortality as 66 per cent. Many women with renal disease abort. In many others the infant dies during labor and delivery. Commonly the babies die in utero during the last month of pregnancy. The prognosis for the fetus is so poor that induction of labor when the fetus is viable is frequently the best procedure. The large placental infarcts that are often found in chronic nephritis, involving from one quarter to one half of the placenta, threaten the life of the fetus during the later months and during labor itself. Premature separation of the placenta occurs in chronic nephritis, although not so commonly as in the pre-eclampsic toxemias.

A woman with proved renal disease should not become pregnant. Her chances of obtaining a living healthy baby are about one in three. The pregnancy will shorten her life, owing to increased kidney damage. There is also the risk of the pregnancy itself with the large incidence of pre-eclampsic

toxemia, as well as other accidents of pregnancy, which these patients do not stand well. Should a patient be seen when she is already pregnant and the renal damage is slight, an attempt may be made to carry her through the pregnancy. The dangers should be explained to her and her husband. She should be carefully watched, given a proper diet and liquid intake, and sufficient rest, and immediately hospitalized if any sign of renal failure appears. In the severe cases, the prognosis for the baby is so poor, and the danger to the mother so great, that abortion should be performed immediately.

### PRE-ECLAMPTIC TOXEMIA

The following definition by Dexter and Weiss<sup>1</sup> is as specific a description of this condition as can be made.

Toxemia of pregnancy (pre-eclampsia and eclampsia) is a humoral and vascular disorder characterized by the appearance, in the second half of pregnancy, of an excess of edema, an elevation of the blood pressure or an increase in the amount of albumin in the urine, or both, above that present before or in the early weeks of pregnancy, and a rapid decrease of edema, lowering of blood pressure, and of the amount of albumin in the urine soon after delivery.

These authors continue with the following statements. Toxemia of pregnancy differs from non-pregnant hypertension chiefly in its relation to water retention. The hypertension of early toxemia is not of renal origin. The toxemia syndrome occurs in mothers with pre-pregnant hypertensive disease as well as in those without. The two most important predisposing factors to development of toxemia are pre-pregnant hypertension (in one third of the cases) and generalized edema (in 85 per cent).

According to Dieckmann<sup>9</sup> the development of pre-eclampsic toxemia is influenced by diet, habits and climate. A hot, wet climate is most favorable for the development of eclampsia. He states that the Mohammedans in India develop more eclampsia than the Hindus or Christians owing to the difference in the amount of meat in the diet. The elimination of sodium chloride, proteins and fats lowers the incidence of severe pre-eclampsia and eclampsia, but not of mild pre-eclampsia.

Eastman<sup>10</sup> gives the statistics of 2418 pre-eclampsic patients over a period of twenty years. In this series there were 92 cases of eclampsia, or an incidence of 3.8 per cent. In eclampsia the maternal mortality was 7.6 per cent, and the fetal mortality 21.7 per cent. The maternal mortality in pre-eclampsia was 0.2 per cent, and the fetal mortality was 6.8 per cent. In twenty years the incidence of eclampsia resulting from pre-eclampsia was reduced from 14.2 to 2.3 per cent. This reduction was due to the earlier recognition of pre-eclampsia and better treatment of that condition.

Cosgrove and Chesley<sup>11</sup> report a series of 1625 cases of pre-eclampsic toxemia. The maternal mortality in this series was 1 per cent. The inci-

dence of premature separation of the placenta was 38 per cent, and that of eclampsia was 5.5 per cent. The total fetal mortality was 171 per cent. The authors state that prophylaxis cannot prevent the actual occurrence of toxemia.

The first appearance of hypertension or albuminuria or both with a sudden gain in weight in the last trimester in pregnancy must be taken to mean the development of pre-eclampsic toxemia. If there is a sudden gain in weight, without the development of hypertension or albuminuria, the possibility of impending toxemia must be considered. A sudden gain in weight in a woman who has been on a reasonable diet usually indicates the presence of visible or invisible edema or of fluid retention.

Dexter and Weiss<sup>1</sup> found generalized edema in 64 per cent of otherwise normal pregnant women. The physical characteristics, distribution, etiology, time of appearance and post-partum disappearance were identical with those of women with toxemia. In 100 patients with edema, the history of previous menstrual headaches and premenstrual edema was twice as frequent as that in patients without edema. Frequently, the appearance of generalized edema was followed shortly by the appearance of toxemia. The incidence of toxemia in women with generalized edema was far greater than that in those without. They were unable to explain the presence of edema by hydrostatic pressure, increased capillary permeability, hypoproteinemia or anemia. A humoral etiology was suspected.

Dieckmann<sup>2</sup> explains the formation of edema by decreased colloid osmotic pressure of serum proteins, increased permeability of capillary walls, and increased capillary pressure. The venous pressure in the leg veins is increased in normal pregnancy, causing a retardation in the absorption of fluid. The capillaries are more permeable. There is a delayed excretion of water and sodium chloride. Edema of the ankles in pregnancy is normal, but other edema is not. Hidden edema is best shown by weight gain, and is often the earliest symptom of toxemia. There is a rapid increase of the incidence of toxemia in excessive weight gain.

The appearance of edema in otherwise normal pregnant women is such a common occurrence that it is frequently not regarded with sufficient gravity. The increased incidence of toxemia following fluid retention is well known. Edema can be partially controlled and sometimes eliminated by proper diet and fluid intake. The fluid intake of any woman developing edema should be restricted. A pregnant woman can be comfortable on as little as 1 liter of fluid in twenty-four hours. The relation of sodium intake to fluid retention is important. It has been shown that the elimination of sodium from the diet often lowers the blood pressure. If salt and sodium compounds are removed from the diet and fluids are limited, most women will excrete a large amount

of the retained fluid and lose a corresponding amount of weight.

Hypertension in pre-eclampsic toxemia (a blood pressure above 140 systolic, 90 diastolic) appears before albumin in the urine in the majority of cases. Hypertension or albuminuria, or both, does not appear before the last trimester of pregnancy. A pregnant woman who has passed uneventfully through the first six months of pregnancy and then develops hypertension presumably has pre-eclampsic toxemia. The blood pressure in this disease runs at a lower level than that in chronic nephritis and essential hypertension. A systolic pressure of 160 in toxemia is a dangerous level. Eclampsia develops at this and at slightly higher levels. This hypertension is due to arteriolar spasm and is not the result of primary kidney disease. This is true only from a clinical standpoint, for it is possible that kidney damage could be demonstrated by more sensitive kidney-function tests than are now available. The level of hypertension must be watched very closely. A steady and rapid rise in blood pressure, even though not great in extent, is an indication of the severe or fulminating type of toxemia, in which eclampsia rapidly develops. In the milder forms of pre-eclampsia, the blood pressure rises slowly and will hold a given level for weeks, or even fall, under the proper medical treatment. When the blood pressure continues to rise in spite of medical treatment the pregnancy should be terminated.

In pre-eclampsia, albumin is the only abnormal finding in the urine. The albumin may appear at first as a very slight trace or may appear rapidly in large amounts. The amount of albumin present has some relation to the severity of the disease but is not so accurate a guide as the hypertension. The small number of cases in which albumin appears first are of the milder form. The presence of casts or blood cells suggests kidney disease rather than true toxemia. In the fulminating type of pre-eclampsic toxemia and in eclampsia, blood cells and casts may appear, owing to secondary damage to the kidney from the toxic process.

As pre-eclampsia progresses, further symptoms are likely to develop. These symptoms usually indicate a more serious and advanced stage of the disease. The cerebral symptoms most often start with headache, which may develop further into dizziness and drowsiness. Visual symptoms, such as diplopia, scotoma and blurred vision, are of serious prognosis. Nausea and vomiting with epigastric pain may be the precursor of eclampsia. When pre-eclampsia is recognized in its earliest stages and responds to proper treatment, these symptoms should not develop, their appearance indicates that the disease is progressing unfavorably.

The etiology of pre-eclampsia is unknown, in spite of much study and investigation. There are many predisposing factors and some fundamental findings

in this disease. Dexter and Weiss,<sup>1</sup> who state that here is some evidence that toxemic patients are more sensitive to the effect of posterior pituitary substance than others, were unable to cause permanent hypertension in rabbits with large and repeated doses of posterior pituitary extract. There were no significant histologic changes in these rabbits. Extracts of placentas from patients with high blood pressure were injected into rabbits without causing any pressor effects, and no such effects were obtained with amniotic fluid. Renin could not be demonstrated in the placentas of patients with increased blood pressure. There was no rise in blood pressure in babies delivered of toxemic mothers. It was concluded that if a pressor substance is present in the mother, it does not cross the placenta. In 16 cases with death of the fetus in utero, 11 mothers showed no improvement of the toxemia until after delivery. These cases indicate that the placenta was the important factor in toxemia.

Dieckmann<sup>9</sup> states that Pituitrin causes a marked rise in blood pressure and suppression of urine in pre-eclampsia. This effect was not observed in hypertensive and renal disease. The thyroid gland is enlarged in the majority of pregnant women. A deficiency in thyroid causes an increase in tissue fluids that contain more proteins. The retention of extracellular fluid may be tremendous. Hypothyroidism produces hypercholesteremia in rabbits, with severe endarteritis of the placental arteries. Colvin and Bartholomew<sup>12</sup> found no cases of toxemia in patients in early pregnancy with a basal metabolic rate of +10 per cent or above. There was an increasing incidence of toxemia as the basal metabolic rate fell. In patients with a rate of -10 per cent or below, there was an incidence of 50 per cent. Many believe that thyroid extract is a good prophylactic against pre-eclampsia.

Smith and Smith<sup>13</sup> have found high levels of chorionic gonadotropin and low estrogenic activity in the blood and urine of toxemic patients. There is also a deficiency of progesterone, the same titer occurs normally just before and during labor. This hormone change occurred weeks before the development of toxemia. The authors believe that fortnightly measurement of the serum gonadotropic hormone, from the fifth month on, will reveal an abnormal rise, eight to ten weeks before the disease becomes clinically apparent, in about 80 per cent of cases. Premature deterioration of placental steroids may be prevented by large doses of diethylstilbestrol. Large doses of estrogenic substance will also increase the production of progesterone. Sufficient clinical work has not been done fully to evaluate this treatment for pre-eclamptic toxemia. Large doses of estrogenic substance after the signs of toxemia have appeared have proved of little value. If a sufficient number of cases were studied and treated early in pregnancy, before the onset of toxemia, the results

could be correlated against the incidence of toxemia in a control group.

More recently Smith<sup>14</sup> has become interested in a toxin isolated from normal menstrual blood. He is impressed by the resemblance of certain physiologic findings in menstruation and toxemia. He mentions retention of water, the decrease of serum diastase, the increased uterine irritability, the systemic disease, which he states is like that of premenstrual and early menstruating endometrium, and, finally, the amelioration of the disease when the uterus is emptied and the removal of the decidua is under way. He has been unable to demonstrate the presence of menstrual toxin in pre-eclampsia or eclampsia. A protective pseudoglobulin has been developed for the treatment of pre-eclamptic toxemia. There was a fall in the blood pressure, as well as a decline in the amount of albumin in the urine, in the patients treated. This work is of great interest because, in many ways, the toxin has the properties necessary for toxemia. However, this toxin has not as yet produced toxemia in animals or human beings, and the clinical results of treatment are still too few and indefinite for any final conclusions.

Cosgrove and Chesley<sup>16</sup> state that definite functional and structural changes in the vascular system, particularly the capillaries and arterioles, are the most universal pathologic tendency in pre-eclampsia. Hertig<sup>16</sup> remarks that toxemia of pregnancy—in all its manifestations, including eclampsia, toxic separation, cortical necrosis, pituitary necrosis and placental degenerations—is part of the same fundamental process. A pathological classification of the separation of the normally implanted placenta fixes the blame for the mortality in this condition, almost, if not wholly, on the toxic variety. Certain placental degeneration that occasionally occurs in all the groups of the American classification, including so-called "minimal toxemia," may cause the death of the fetus in utero. He stresses the fact that some babies due to die in utero from this cause may be saved by prompt action when fetal growth has ceased. The smaller the infant, the more certain it is that placental degeneration exists.

Tenney and Parker,<sup>17, 18</sup> in a study of the histopathology of the placenta in pre-eclamptic toxemia and eclampsia, found a placental lesion characteristic of this disease. The lesion consists primarily of a premature aging of the placenta, which takes place in the syncytium of the small villus buds. A normal full-term placenta will show from 10 to 50 per cent degenerated buds. A count of one hundred to two hundred villus buds should be made for an accurate determination. In pre-eclampsia and eclampsia this degeneration involves from 50 to 100 per cent of the syncytial buds. It is extremely important that the actual age of the placenta be taken into account. Syncytial degeneration in the normal placenta does not begin before the eighth month and, as stated

above, does not reach over 50 per cent at term. Therefore, in a seven-month placenta, there should normally be no syncytial degeneration. The finding of a moderate amount (about 25 per cent) of syncytial degeneration in a seven-month placenta would be indicative of pre-eclamptic toxemia, whereas in a full-term placenta, there would have to be over 50 per cent to indicate toxemia. In essential hypertension, uncomplicated by toxemia and renal disease, this typical degeneration is not found. The amount of syncytial degeneration observed in toxemia is relative to the severity of the disease. In 100 cases of pre-eclamptic toxemia, pronounced placental lesions were noted in 60 per cent. In 90 per cent of these cases albuminuria was present. In the other 40 per cent, which showed less pronounced lesions, albuminuria was present in less than half. This suggests that placental damage begins before clinical symptoms appear. If the syncytium is regarded as similar in function to the glomerular epithelium of the kidney, the destruction of this epithelium, together with circulatory congestion, may explain the high fetal mortality in this condition.

The renal changes in toxemia are best described by Bell.<sup>19</sup> The glomeruli are slightly enlarged. The lumens of their capillaries are narrowed, and sometimes completely closed, so that they contain but few erythrocytes. The decrease of the capillary lumen is caused mainly by thickening of the capillary basement membrane. The increase in the endothelial cells is variable. Dexter and Weiss,<sup>1</sup> in a study of 25 cases of fatal eclampsia that came to autopsy, found the combination of microscopical changes observed in the kidneys specific and characteristic for toxemia in all cases. The lesions were primarily degenerative, and the term "glomerulonephrosis" seemed most suitable. These changes are sometimes noted in mild pre-eclampsia.

The typical liver lesion of eclampsia was found in only 50 per cent of autopsies at the Mallory Institute of Pathology. This lesion consists of hemorrhagic necrosis of the peripheral portion of the liver lobules. When this lesion is found, it is definitely specific for eclampsia. In this connection the work of Ingerslev and Teilum<sup>20</sup> is of interest. They performed aspiration biopsies on the livers of normal pregnant women and on those with pre-eclamptic toxemia and eclampsia. There were no changes in the livers of the former and no histologic or chemical grounds to maintain the concept of a pregnancy liver. In pre-eclampsia the authors also found no change. In eclampsia peripheral hemorrhagic necrosis was observed in 50 per cent of cases. The liver damage in the patients with toxemia appears to have been a terminal result, not a cause, of severe disease.

Dieckmann<sup>8</sup> describes extensive cerebral hemorrhage in 15 to 20 per cent of autopsies in deaths from eclampsia.

The physiochemical changes in the blood and urine of women with pre-eclamptic toxemia have been thoroughly studied by many investigators. Unfortunately, there is no physiochemical test that is pathognomonic of this disease. The nonprotein nitrogen of the blood is not high in pre-eclampsia. It is only in the later stages and in eclampsia that a rise is found. Stander<sup>7</sup> describes a high blood ureic acid which is an important aid in the differentiation of pre-eclamptic toxemia, but it is not a consistent finding. Dieckmann<sup>8</sup> describes a blood concentration in severe pre-eclampsia and eclampsia, but this is not found in the mild cases.

Eastman<sup>10</sup> gives four objectives in the treatment of pre-eclamptic toxemia: prevention of convulsions, prevention of residual hypertension, delivery with minimal trauma and yet in a manner that will not handicap the patient in future pregnancies, and delivery of a living child.

Prophylaxis is the first and most important treatment. Every pregnant woman should be under medical care from the time that she first knows she is pregnant. She should be on a high-protein diet including plenty of meat, fish, eggs and milk. She should have a low-fat and low-carbohydrate intake. Salt and other sodium compounds should be limited to a minimum. Fluids should be allowed in amounts necessary for comfort, but excessive fluid intake should be avoided. The weight should be carefully followed, the weight gain for the entire pregnancy should be limited to 20 pounds. If the patient becomes overweight, she should try to reduce. In cases of excessive weight gain, the patients should be put on a diet of 1200 calories. If the patient does not co-operate and obtain an immediate weight loss, she should be hospitalized, and the weight reduced under supervision. She should be given iron and vitamins during the entire pregnancy and should have sufficient rest and a moderate amount of exercise. Proper and regular bowel elimination is important.

If hypertension or albuminuria, or both, develops in the last trimester of pregnancy, the patient should first be treated by medical means. She should be confined to bed and put on a high-protein, fat-free diet. All salt and sodium must be eliminated from the diet. If there is visible edema or an increase in weight, 1 liter of fluid daily should be prescribed, and one good cathartic and sufficient laxative for a daily bowel movement should be given. A sedative is helpful. Frequently, a patient improves and can be up and about on a restricted regime.

If the patient does not respond to the treatment outlined above she must be hospitalized. The same regime is continued under hospital care, with the possible addition of intravenous hypertonic glucose. Blood-pressure readings must be taken frequently, a careful record kept of the fluid intake and output, and daily catheterized specimens exam-

ed in the laboratory. If, in spite of treatment, the blood pressure continues to rise and the albuminuria increases, termination of the pregnancy is indicated. The method used to terminate the pregnancy must depend on the severity of the disease and the condition of the patient. In the acute, fulminating type of toxemia occurring in primiparas, cesarean section is usually the method of choice. Even in some multiparas with acute exacerbation of symptoms and an unfavorable cervix, cesarean section may be indicated. In milder cases and even in severe cases of multiparas in which the cervix is favorable, rupture of the membranes and delivery from below may be the best procedure. However, each case must be judged by itself, and the attending obstetrician should take the whole situation into consideration before making his decision.

### ECLAMPSIA

Eclampsia is the final stage of an unchecked pre-eclampsia. Many cases of pre-eclampsia are not sufficiently severe to develop into eclampsia, but many other cases do, if not properly treated. Eclampsia is the development of convulsions or coma, or both, following pre-eclampsia. Not all cases of coma or convulsions in pregnancy are due to eclampsia. Among the causes of convulsions that must be differentiated from eclampsia are epilepsy, hysteria and diabetes. Also, various cerebral lesions must be ruled out. The convulsions of eclampsia may appear before, during or after labor. Typically, a patient has a series of convulsions separated by periods of lethargy. Accompanying the convulsions is marked hypertension and albuminuria. Casts—hyaline, epithelial and granular—may appear in the urine. There is a marked reduction in the output of urine and sometimes complete suppression. DeLee<sup>8</sup> gives the maternal mortality of eclampsia as 13 per cent, with a fetal mortality of 40 per cent.

The treatment of eclampsia should be preventive. The uterus should be emptied before the convulsions appear. Once the convulsions have appeared, the treatment is primarily conservative. On the basis of the original Stroganoff treatment, sedation and rest are the primary objectives. The patient should be put in a quiet and dimly lighted room. The eyes should be covered, and the ears blocked with cotton. She should be well sedated with morphine and chloral hydrate. Chloroform is still used to control the convulsions. Magnesium sulfate may be given intravenously in a 20 per cent solution. Hypertonic glucose may be administered intravenously to stimulate kidney excretion. Veratrine is recommended by Kellogg.<sup>21</sup> Willson<sup>22</sup> states that the administration of veratrine causes a marked suppression of urine in pre-eclampsia. Dieckmann<sup>9</sup> warns of the danger of vascular collapse from this drug.

The treatment of the disease is the fundamental problem in eclampsia, and no attempt at delivery should be made during the convulsive stage. Cesarean section is definitely contraindicated. Frequently, labor begins, and delivery is normal. In other cases, when the convulsions are under control, labor may be induced, and the patient allowed to progress through labor. Rupture of the membranes is the simplest and surest way of induction, and the use of the bag is not recommended. The patient often shows some improvement after the rupture of the membranes. The labor should be allowed to proceed at its own speed, and no interference should be considered until the cervix is fully dilated. Frequent complications of eclampsia are anuria, pulmonary edema and sepsis.

The end results of pre-eclampsia and eclampsia show permanent damage in many cases. According to Kellogg<sup>21</sup> the residual lesion from the former is hypertension, which was found in 50 per cent of cases. After eclampsia, hypertension was present in 60 per cent. Glomerulonephritis did not occur in any patient as the result of eclampsia. The older the patient, the greater the parity, the higher the blood pressure during pregnancy and the longer the duration of the illness, the greater the liability to the ultimate occurrence of hypertension.

Dexter and Weiss<sup>1</sup> believe that hypertension follows toxemia of pregnancy in 25 per cent of patients who have had a normal blood pressure before pregnancy, and an elevation in the percentage of women who have had hypertension before pregnancy. The occurrence of sustained post-partum hypertension depends more on the duration than on the severity of the toxemia. Sustained hypertensive vascular disease may be initiated by toxemia of pregnancy.

Reid and Teel<sup>23, 24</sup> report that in 235 cases previously diagnosed as mild pre-eclampsia, six months to three years after delivery, no patients had renal impairment. In 21 per cent the systolic pressure was over 150. Of 89 patients with hypertension before pregnancy, 44 per cent had a higher blood pressure six months to three years after delivery than when first seen.

Browne and Dodds<sup>25</sup> report 400 toxemic patients studied six to twelve years after delivery. Fifty-one per cent had hypertension. They found, as Kellogg did, that older patients with greater parity, higher blood pressure and longer duration of illness were more likely to develop hypertension. There were no cases of glomerulonephritis as a result of toxemia. Sixty per cent of the patients had hypertension after eclampsia. The authors suggest that patients who develop residual hypertension after pre-eclamptic toxemia and eclampsia have a familial tendency to the disease, which pregnancy has merely revealed. The onset of pregnancy hastens the disease, which sets in at an earlier period than it would otherwise have done.



## SUMMARY

Essential hypertension of the benign type is not seriously influenced by pregnancy. There is a greater incidence of pre-eclamptic toxemia in these patients than in normal pregnant women. A superimposed toxemia is a serious danger.

Pregnancy is a dangerous complication of renal disease, resulting in increased kidney damage. Superimposed toxemia increases this damage. Pregnancy should not be permitted in severe renal disease.

Pre-eclamptic toxemia is best treated by proper prophylaxis. Excessive weight gain is a predisposing cause. If the toxemia does not respond to medical treatment, the uterus should be emptied before convulsions develop.

Eclampsia should be treated conservatively.

Permanent hypertension after toxemia has a definite relation to the length of time the disease persists, as well as to its severity.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 34011

#### PRESENTATION OF CASE

A seventy-eight-year-old man entered the hospital complaining of an ache in the abdomen of three weeks' duration.

For six weeks he had noted ankle edema. Soon he developed swelling of the abdomen, anorexia, mild abdominal distress, exertional dyspnea, and watery, black stools four times a day. In this period he lost 8 pounds. Previously his health had been excellent. He denied orthopnea, chest pain, cough, jaundice or

excessive alcohol intake. He admitted taking a glass of wine with meals. For six months the patient had suffered from incontinence, frequency, nocturia, weak stream and difficulty initiating the stream.

Physical examination revealed a well developed but emaciated, elderly man in no distress. No jaundice was noted. A Grade I aortic systolic murmur was heard. Abdominal examination showed ascites, a liver edge palpable 3 cm. below the costal margin and slightly tender, bilateral inguinal hernias, hemorrhoids and a prostate one and a half times the normal size. There was +++ pitting edema of the ankles and lower legs.

The temperature, pulse and respirations were normal. The blood pressure was 175 systolic, 85 diastolic.

Examination of the blood disclosed a red-cell count of 5,900,000, with 16.5 gm. of hemoglobin, and a white-cell count of 8400, with a normal blood smear. The urine contained no albumin, sugar or bile, and had a specific gravity of 1.020. Two stools were guaiac negative. The total protein was 5.96 gm. per 100 cc., with an albumin-globulin ratio of 1.41. The nonprotein nitrogen was 30 mg. and the cholesterol 156 mg. per 100 cc., the esters being 85 mg. per 100 cc. The time was 27 seconds (normal, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 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cephalin-flocculation test + in twenty-four and +++ in forty-eight hours

A barium-enema examination was negative. Chest films showed collapse of the right upper lobe, which contained multiple small cavities. There was old pleuritis at the right base and apex. The trachea and upper mediastinal structures were displaced to the right.

Paracentesis produced 3230 cc of bloody fluid with 430,000 red cells and 150 white cells per cubic millimeter and a specific gravity of 1.010. No tumor cells or tubercle bacilli were found in the ascitic fluid.

Cystoscopy showed no cause for the urinary symptoms except a slightly enlarged prostate.

The patient became quite jaundiced, and the ascites recurred. On the fifteenth day bleeding into the skin occurred, and 200 cc of blood was aspirated from the mouth. He died the following morning.

#### DIFFERENTIAL DIAGNOSIS

DR MYLES P. BAKER: We are dealing with an elderly patient with ascites and ankle edema of relatively short duration (three to six weeks) and a noteworthy absence of symptoms, except for those attributable to prostatic hypertrophy. There was a history suggestive of bleeding from the upper gastrointestinal tract. The important negative findings on physical examination seem to me to be the absence of evidence of congestive heart failure, the absence of any abnormal physical findings, particularly over the right upper lobe, the absence of a palpable spleen or spider angiomas, and also the lack of a really large liver. The liver edge was said to be palpable 3 cm below the right costal margin, but that is only about two fingerbreadths, if that, and we do not know where the upper border of the liver was. Possibly, the finding represents a low liver rather than a large one. There is no note on rectal examination regarding whether any firm mass was palpable in the rectal shelf. Presumably it was not, or it would have been mentioned. But that is an important finding in an elderly person with ascites.

The laboratory studies revealed certain important features. First of all, there was no anemia—or surprisingly little for a man in whom liver disease is suspected. There was no element of renal insufficiency, which is significant in a man who had been having urinary symptoms that made him uncomfortable rather than ill. There was no bile in the urine, which tallies with the finding of no detectable icterus. We have no evidence on examination for bleeding into the gastrointestinal tract. The serum protein of 5.96 gm per 100 cc is barely below the normal range, and the serum albumin can be calculated as  $\pm 3.5$  gm per 100 cc, which is slightly below the normal range but not so low as one would expect to be one of the chief causes of a large accumulation of ascitic fluid. The globulin of 2.4 gm

per 100 cc is at the upper limits of normal and not so high as one would expect in the usual case of cirrhosis of the liver with ascites. The normal blood cholesterol levels are about what one would expect, and I do not quite see why the test was done in the first place. There was no significant decrease in the esterified portion, as one sees with acute liver-cell damage. The prolonged prothrombin time is important, but it was not within the danger level that causes hemorrhage. Finally, the cephalin-flocculation test of +++ in forty-eight hours is consistent with liver-cell damage. The one test that I should expect that the house officers would have recourse to, the bromsulfalein-excretion test, apparently was not done. The finding of bloody ascitic fluid, of course, sticks out in this protocol like a sore thumb. It has always been and is still a very rare finding in cirrhosis of the liver and immediately directs one's attention toward the possibility of a cancerous process involving the peritoneum. X-ray examinations were subsequently done, probably with this in mind. A barium enema revealed no evidence of cancer in the cecum, sigmoid or rectum. X-ray examination of the chest revealed an abnormal finding, a collapsed right lower lobe with multiple small cavities, which I think I shall ask Dr Wyman to describe.

DR STANLEY M. WYMAN: The collapsed right upper lobe lies in this location at the apex, with what appears to be thickened pleura over the apex. Multiple small areas of decreased density are present that may represent dilated bronchi scattered throughout this rather shrunken lobe. The trachea is deflected considerably toward the right. The right leaf of the diaphragm is moderately elevated, and there is what may be a small amount of fluid or thickened pleura in the costophrenic angle. The heart shadow is retracted a little toward the right, with a prominent left ventricle, a tortuous aorta and some calcification, which is all in keeping with the hypertension. The lung fields, except for the right upper lobe, show no definite localized disease. I can trace the bronchi rather well in both lung fields. I cannot entirely exclude obstruction of the right upper-lobe bronchus, however. A barium enema is described, but I can only find incomplete films of that examination. A gastrointestinal series was apparently done, although we have no report of it, but it may be of help to Dr Baker. The esophagus can be seen very fragmentarily, and there is no definite evidence of esophageal varices. The stomach appears to be within normal limits. I believe that there is probably an enlarged liver and possibly a large spleen.

DR BAKER: Do you consider these areas of diminished density in the collapsed lobe compatible with dilated bronchi rather than cavities?

DR WYMAN: Yes, or they could be small bronchiectatic cavities.

DR BAKER In a further search for possible sites of carcinoma, a cystoscopy was done, and apparently carcinoma of the prostate excluded. The patient went on to die in two weeks, a short course of seven weeks' illness in all, with evidence terminally of bleeding in the gastrointestinal tract and the skin, and deepening jaundice—a picture that we consider compatible with a cholemic death. Against the diagnosis of cirrhosis of the liver, again, are the bloody ascitic fluid, the serum albumin level of 3.5 gm per 100 cc in the presence of ascites, the absence of anemia, the absence of splenomegaly to be found in probably two thirds of such cases of cirrhosis and ascites and the absence of collateral circulation found in 50 per cent of such cases and of spider nevi. The patient was old for cirrhosis.

The question arises whether the findings in the chest by x-ray examination are compatible with a diagnosis of bronchiogenic carcinoma. I cannot rule out the presence of a bronchostenotic lesion involving the right upper-lobe bronchus. With such a lesion I would expect more evidence of active infection distal to the tumor. However, it is interesting to remember that in bronchiogenic tumors the first symptoms may be those of metastases, distant metastases, rather than mere chest pain and blood-streaked sputum. Bronchiogenic carcinoma frequently metastasizes by way of the blood stream and involves the liver in about 35 per cent and the peritoneum in 4 to 5 per cent, and the abdominal lymph nodes in a third of the autopsy cases. The possibility of such an origin of carcinoma must therefore be borne in mind in this case. I have never seen such a situation, however,—ascites as the presenting symptom with bronchiogenic carcinoma,—possible though it may be, and I could find no reference to it in the literature. I am inclined to look upon the findings that Dr Wyman has demonstrated in the chest x-ray film as an old story in an elderly man, due probably to inflammatory disease involving the upper-lobe bronchus with atelectasis, representing an inactive process.

The question of a primary hepatoma arises in this patient, who presented grossly bloody ascites, which is a common finding in the presence of this rather rare tumor, probably in two out of three malignant hepatomas such grossly bloody ascites is found. We have very little evidence for the presence of cirrhosis of the liver, which is frequently associated with primary hepatomas, and I think that the absence of such an antecedent history of cirrhosis and of a large, firm, hard liver are rather important points against the diagnosis of hepatoma. It is a rare tumor. Moreover, we have no evidence of tumor elevating the right leaf of the diaphragm—a finding that I have seen in cases of hepatoma. In considering a possible site of origin for what I take to be metastatic carcinoma involving the parenchyma of the liver and peritoneum, I come then by exclusion to carcinoma of the body of the

pancreas. The patient had none of the characteristic backache, left sided or midline, that such persons with carcinoma of the body of the pancreas have. This tumor frequently involves the peritoneal surface as well as the liver and gives rise to progressive swelling of the abdomen as the initial symptom, closely followed by edema of the ankles, jaundice and the clinical picture presented in this case. Perhaps chiefly because I have seen it do so, I shall choose it as the most likely diagnostic probability in this man who presented bloody ascites as the outstanding abnormality and who gave, for reasons noted above, no grounds for the diagnosis of cirrhosis of the liver.

DR CHESTER M. JONES Is it not true that in the lower film it would be impossible to state that the liver or spleen was enlarged because there is so much fluid and homogeneous density?

DR WYMAN Yes

#### CLINICAL DIAGNOSIS

Peritoneal carcinomatosis

DR BAKER'S DIAGNOSIS

Carcinoma of body of pancreas

#### ANATOMICAL DIAGNOSES

*Hepatoma, with extension into portal and hepatic veins*

*Portal cirrhosis of liver, inactive*

*Bronchiectasis, right upper lobe*

*Benign prostatic hypertrophy*

*Arteriosclerosis, generalized*

#### PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY I think that this case is a very blid one from the diagnostic point of view. The diagnosis was established a day or two before death by peritoneoscopy, but we believed that there would be no fun in discussing it if we gave the results of the peritoneoscopic biopsy of the liver. It showed the characteristic picture of hepatoma. At autopsy the right lobe of the liver was completely replaced by tumor, which had invaded extensively both the portal and the hepatic venous systems. This is characteristic of primary liver-cell carcinomas. There were no distant metastases. The spleen was not enlarged, weighing only 170 gm. There were no esophageal varices. There was, however, in the left lobe of the liver, evidence of an old burnt-out cirrhosis, such as is almost invariably found in patients who develop hepatoma. We have had only 1 case in this laboratory of primary liver-cell carcinoma not associated with cirrhosis. That was in a ninety-five-year-old woman. Dr Kernahan, what is your experience in this regard?

DR JAMES W. KERNAHAN We have just gone over our cases of carcinoma of the liver at the Mayo Clinic and found 75 per cent of the hepatomas associated with cirrhosis. Twenty-five per cent were not, but those were usually in children.

DR. MALLORY Cholangiomas in general are less frequently combined with cirrhosis than the hepatomas

Two other findings of possible importance were a bronchiectasis in the right upper lobe and a moderate hypertrophy of the prostate

DR. BAKER Do you often find pain in the right upper quadrant in patients with hepatoma?

DR. MALLORY One does, but one also finds pain in the right upper quadrant in patients with cirrhosis who have no tumor. There is no explanation for the pain whatsoever

## CASE 34012

### PRESENTATION OF CASE

A nineteen-year-old boy was admitted to the hospital because of difficulty in urination.

Three months before entry he began to notice an "itch" in the anus that gradually changed to a dull ache "inside," above the anus and to the left. This pain was worse on bending over. It finally became so severe that he was unable to lie on his back. One month later, while at work, he had a sudden episode of dizziness and "pins-and-needles" sensation all over. This passed off in an hour but left him weak, and he did not wholly recover for two or three weeks. Eight days before entry he was unable to urinate although the bladder felt distended. He had to be catheterized. Two days later he again was unable to void and had to be catheterized. This time he had severe back pain as well. In the last five days before admission he had difficulty in urination, relieved somewhat by Sitz baths. The back pain was intermittent and associated particularly with retention. He had mild constipation and a weight loss from 135 to 126 pounds in the three-month period. There was no history of frequency, nocturia, stones or venereal disease, no paresthesias of the legs and no disorder of gait.

Physical examination revealed a well developed, nervous, apprehensive boy. He had bilateral, small, soft, palpable, anterior and posterior cervical lymph nodes. There was a left lumbar scoliosis. On rectal examination there was a hard, fixed, irregularly rounded mass about 2 cm in diameter at the junction of the sacrum and coccyx, to the right of the midline. It was questionably tender. A complete neurologic examination was negative, except that the ankle jerk was less active on the left side.

The temperature was 97°F, the pulse 90, and the respirations 20. The blood pressure was 115 systolic, 60 diastolic.

The white-cell count was 10,000, with 80 per cent neutrophils. The red-cell count was 4,570,000. The fasting blood sugar was within normal limits, and a blood Hinton test and a routine urine examination were negative. The cerebrospinal fluid was acellular, and the protein was 36 mg per 100 cc.

An intravenous pyelogram showed normal kidneys, with prompt excretion of the dye on both sides. The bladder was large and emptied incompletely. There was no definite abnormality of the pelvis. There was questionable loss of trabeculation of the right distal sacral segments, although this area was partially obscured by bowel contents. A myelogram showed a free flow of Pantopaque from the ninth dorsal body to the cul-de-sac, without evidence of defect. A barium enema showed no intrinsic disease or displacement of the rectum or sigmoid. No mechanical obstruction was seen by cystoscopy or panendoscopy. X-ray examination of the chest was negative.

While in the hospital the patient was treated with tidal drainage of the bladder and sulfadiazine. He had a few episodes of "stabbing pains" just to the left of the anus, radiating anteriorly through the perineum. These were associated with a constant grimace, and he held himself rigid on the left side.

An operation was performed on the fourteenth hospital day.

### DIFFERENTIAL DIAGNOSIS

DR. ROY E. MABREY This patient presented a history of intermittent pain in the low back extending into the perineum. He also had difficulty in urination. The onset was gradual, and the symptoms increased in severity.

The itch noticed in the anus may have resulted from irritation of a nerve, or it may have been that the patient's attention was drawn to this area. The type of pain characterized by a dull, intermittent ache could have resulted from pressure due to inflammation or to neoplasm.

The episode of dizziness with "pins-and-needles" sensation may have been due to a reflex reaction with a concomitant fall in blood pressure.

The mechanism of emptying the bladder became more and more disturbed. Eight days before admission and again two days later the patient had to be catheterized. There is no note of how much urine was obtained, but analysis was normal when he entered the hospital. An intravenous pyelogram showed no evidence of hydronephrosis, and there was enlargement of the bladder with incomplete emptying. Obstruction to the outflow, such as that due to stricture, stone or an enlarged prostate, would have caused spasm of the bladder and given rise to considerable pain. The atonic nature of the bladder, or the dysuria, points to some involvement of its nerve supply.

Neurologic examination revealed no abnormality, except that the ankle jerk was less active on the left than on the right. There were no sensory changes or disorder of gait. A lumbar puncture revealed normal fluid, but no mention was made of the dynamics. A myelogram was normal, however. These findings tend to eliminate an intrathecal lesion. The change in bowel habit with constipation

was not accompanied by diarrhea, bleeding or tenesmus. It may have been due to restricted food intake and reduced activity.

Physical examination disclosed soft lymph nodes in the neck. The axillae and groins are not mentioned. Examination of the blood showed a white-cell count of 10,000, with 80 per cent neutrophils. This is within normal limits but might point toward an inflammatory process. Other studies, including the sedimentation rate, calcium, phosphorus and alkaline phosphatase might have been of some help.

On rectal examination there was a hard, fixed, irregularly rounded mass about 2 cm in diameter at the junction of the sacrum and coccyx. The problem is to determine the nature of this fixed mass, on the assumption that it could account for all the symptoms.

In discussing the possibilities, I should like to list four general headings: congenital, traumatic, infectious and neoplastic.

Spina bifida, the most common of the congenital lesions in this region, would manifest itself at an earlier date and a defect should be noted by x-ray examination. A cyst, such as a dermoid or a teratoma, which often contains teeth or bone, would also show on the x-ray film.

There was no history of injury, and one severe enough to cause these symptoms would have caused other signs.

A perirectal abscess occurs above the levator ani muscles and is quite rare. Also, the patient is likely to have chills and fever with a high white-cell count. Osteomyelitis would give more constitutional reaction, with a high white-cell count. Tuberculosis in this area is rare without widespread involvement. The negative blood Hinton test probably rules out syphilis.

In my opinion the mass palpable on rectal examination was neoplastic in origin. It is not likely that it arose in the rectal wall. There was no ulceration of the mucosa, which would have been accompanied by bleeding and tenesmus. Any ulceration could have been detected with a sigmoidoscope, although barium studies might not have outlined it. A neurogenic tumor has to be considered and cannot be ruled out. Since the tumor arose in the vicinity of the sacrum, primary bone tumors have to be thought of. Although Ewing sarcoma has a predilection for the shaft of long bones and half the cases occur before the age of fifteen years, it may occur in the sacrum and at another age. It is likely to be accompanied by elevation of temperature, and x-ray examination usually shows new bone being deposited in layers. Osteogenic sarcoma may occur in any bone, but it is found most often in the long bones. The greatest incidence is at the age of twenty, and the pain is usually constant; the x-ray findings are more definite than they were in this case. A chondroma or chondrosarcoma is a

possibility. Metastatic disease is not likely to produce a single projecting lesion such as this.

There are two tumors left to be considered that are not too infrequent in this area: chordoma and benign giant-cell tumor. Chordoma arises from remnants of the fetal notochord. Its growth is very slow, and pain is the first symptom. A study of 150 cases reported in 1935 revealed that no patient with a chordoma in the sacrococcygeal region sought medical advice in less than four months after onset.\* The average age of the patients was fifty years, although 6 cases occurred between twenty and thirty years. Considerable destruction of bone had taken place before the patient consulted a physician.

Giant-cell tumor is usually slowly growing. The presenting symptom is pain, which is intermittent in character. The greatest incidence of occurrence is between the ages of fifteen and twenty-five. Destruction and regeneration of bone give a "soap bubble" roentgenogram.

The presence of intermittent ache and dull pain of three months' duration in a boy of nineteen, with no elevation of temperature, point to a neoplastic process. The interference with bladder function indicates that the growth occurred in proximity of the nerves of the bladder. In the absence of good x-ray films, which are usually very characteristic, I shall put giant-cell tumor of the sacrum as my first choice.

#### CLINICAL DIAGNOSIS

Chondrosarcoma of sacrum

DR. MABREY'S DIAGNOSIS

Giant-cell tumor of sacrum

#### ANATOMICAL DIAGNOSIS

Ewing sarcoma of sacrum

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: This patient was seen by many consultants, and the consensus was that he had a sacrococcygeal tumor, with chondrosarcoma leading the list. It was not considered advisable to attempt a biopsy through the rectum. The lower half of the sacrum and the entire coccyx were excised en bloc by Dr. W. J. Mixer. When received in the Pathology Laboratory, the specimen showed replacement of a portion of the sacrum by reddish-gray tissue, which on microscopical examination proved to be an Ewing sarcoma.

Although there was no gross evidence of residual disease at operation, tumor was found in the soft tissues microscopically. The patient was therefore given 6000 r of x-ray therapy, 1500 kilovolts over a 15-by-15-cm. field being given during a period of six weeks. When seen two months later, he already had pulmonary metastases.

\*Mabrey R. E. Chordoma: study of 150 cases. *Am. J. Surg.*

accepted as a matter of course among industrial workers, there can be no surprise that young women of high caliber and intelligence are reluctant to go through a period of intensive training to prepare themselves as nurses. All solutions to the problem, therefore, depend essentially on the fact that the nursing profession must be made more attractive.

Thus, physicians can do much to influence qualified young women in their choice to enter this most vital profession, and efforts on the part of women's auxiliaries can be equally effective. But nurses must first be accorded the recognition and benefits commensurate with their professional status, certainly, they are justified in demanding the rights taken for granted by even unskilled workers — better pay for fewer hours of work, social security, sick leave, vacation pay and adjustment for night and overtime work. Suggestions of substituting practical nurses for registered professional nurses to take over the major part of ordinary bedside care<sup>2</sup> and for greater utilization of nurse's aides offer some hope for a solution of the problem, although such proposals appear to underestimate the danger of nursing care of inferior quality at a time when the public is demanding the highest standards in all forms of medical care. Finally, Congress must be persuaded to continue the exemption, inaugurated during the war years and permitting registration of nurses at the age of twenty, to the requirement of a minimum age of eighteen years set by the Board of Registration of Nurses for admission to nursing schools. But even girls who graduate from high school at the age of seventeen could not be blamed for seeking professions offering better pay and better working conditions than those offered by a nursing career.

Physicians and their wives are urged to make every possible contribution to the campaign of the Student Nurse Recruitment Committee. The medical profession and hospital administrations are also urged to co-operate by exerting every effort to obtain for nurses their proper recognition and economic stability.

#### REFERENCES

- 1 Editorial. Forceful challenge. *New York Herald Tribune* November 29, 1947.
- 2 Fishbein, M. Nursing as career. *Hygia* 25:915, 1947.

## LIQUIDATION OF THE EMERGENCY MATERNITY AND INFANT CARE PROGRAM

A NOTICE elsewhere in this issue of the *Journal* calls attention to the liquidation of the Emergency Maternity and Infant Care Program in the United States. In Massachusetts there are many outstanding physicians' bills, some dating back to the beginning of the program. It is important that all outstanding medical bills be submitted immediately. The expanded staff necessary to carry this program is now being contracted because of the cessation of administrative funds, therefore, it will become increasingly difficult, and will take a longer time, for approval and payment of bills. It is to the physician's own interest to render his bills as soon as possible.

### ROBERT N. NYE MEMORIAL FUND

The American Cancer Society, Incorporated (Massachusetts Division), announces that the Robert N. Nye Memorial Fund is in excess of \$2385.

### MASSACHUSETTS MEDICAL SOCIETY DEATHS

**CURTIS** — Charles L. Curtis, M.D., of Salem, died on December 11. He was in his sixty-second year.

Dr. Curtis received his degree from Bowdoin Medical College in 1909. He was for many years senior member of the surgical staff at the Salem Hospital, and was a fellow of the American College of Surgeons and the American Medical Association and a member of the New England Surgical Society.

A daughter, two sons and several grandchildren survive.

**GREENWOOD** — Arthur M. Greenwood, M.D., of Boston, died on December 14. He was in his seventy-first year.

Dr. Greenwood received his degree from Harvard Medical School in 1902. He was formerly a member of the staffs of the Massachusetts General, New England Deaconess and Palmer Memorial hospitals. He was a member of the New England Dermatological Society, American Dermatological Association and American Academy of Dermatology and Syphilology and was a fellow of the American Medical Association.

His widow and two stepsons survive.

### MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

#### LIQUIDATION OF EMERGENCY MATERNITY AND INFANT CARE PROGRAM

Physicians who have outstanding bills for pediatric and obstetric care given to Massachusetts mothers and children under the Emergency Mater-

nity and Infant Care Program are urged to submit these bills for payment, immediately, since the program is now in the process of liquidation.

A separate bill and a statement of services rendered must be submitted for each patient for whom compensation has not been received. If necessary, additional copies of the required blank forms that must be completely filled out by the physician — "Physician's Statement of Obstetric Services Rendered" or the "Physician's Statement of Pediatric Services Rendered" — may be obtained from the Division of Maternal and Child Health, 73 Tremont Street, Boston. The bill must be presented on the physician's regular, printed statement form.

## STATE PLAN FOR THE ADMINISTRATION OF HOSPITAL SURVEY AND CONSTRUCTION ACT

The State Plan for the administration of Public Law 725 (Hospital Survey and Construction Act) has been approved by the State Advisory Council and the Public Health Council of the Massachusetts Department of Public Health and, following a public meeting on November 12 in Boston, by the Surgeon General of the United States Public Health Service.

In the Massachusetts Plan, existing general hospitals were distributed among seventy service areas. The most recent survey of hospital beds in Massachusetts indicates that there are 18,224 general-hospital beds, 1,100 beds for patients with chronic diseases, 3,604 beds for patients with tuberculosis and 21,102 beds for mental patients. In accordance with the federal formula as given in Public Law 725, the number of beds needed according to the categories mentioned above is, respectively, 23,829, 9,136, 4,408 and 22,840.

A priority schedule based primarily on the percentages of need met by existing facilities was established, and all general hospital construction will take place in accordance with this schedule. Top rank in the list was given to seven hospital areas within the Commonwealth — namely, Athol, Needham, Medford, Northbridge, Woburn, Milford and Ipswich. It is expected that within the first year of the program it will be possible to make two or three grants among the applicants having a Group A priority.

An allotment will also be designated for the construction of hospital units for chronic diseases. The metropolitan areas of the Commonwealth, including Boston, Springfield, Worcester and Pittsfield, will have first priority in this category. Finally, 20 per cent of the total allotment for the first year will be allocated for the construction of health centers.

## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER 1947

DISEASES	RÉSUMÉ		
	NOVEMBER 1947	NOVEMBER 1946	SEVEN YEAR MEDIAN
Chaserooid	5	2	2*
Chicken pox	753	770	1025
Diphtheria	18	61	17
Dog bita	636	664	611
Dysentery bacillary	21	3	22
German measles	60	61	59
Goosepox	234	378	378
Granuloma inguinale	0	0	0*
Lymphogranulosis venereum	0	0	1*
Malaria	5	15	15
Measles	153	691	691
Meningitis, meningococcal	5	6	12
Meningitis, Pfeiffer bacillus	3	5	5
Meningitis, pneumococcal	4	1	4†
Meningitis, staphylococcal	1	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	0	1	1†
Meningitis, undetermined	7	1	3†
Mumps	461	306	523
Parasmosis, lobar	48	61	193
Poliomyelitis	15	54	24
Salmonellosis	8	14	7
Scarlet fever	305	192	704
Syphilis	215	203	407
Tuberculosis, pulmonary	222	224	217
Tuberculosis, other forms	12	12	16
Typhoid fever	1	2	1†
Undulant fever	3	5	4†
Whooping cough	648	598	661

\*Three-year median

†Five-year median

### COMMENT

Diseases with incidence above the seven year median are diphtheria, dog bite, German measles, salmonellosis and pulmonary tuberculosis.

Diseases below the seven year median are chicken pox, malaria, measles, meningococcal meningitis, mumps, lobar pneumonia, poliomyelitis and scarlet fever.

Poliomyelitis dropped to less than one third of the prevalence of November, 1946, the peak having occurred nearly a month earlier this year than last.

Although diphtheria did not maintain the sharp upward trend of October, the seasonal increase is certain to continue with a peak some time in December, January or February.

Measles is at the lowest prevalence for November since 1906, and chicken pox at the lowest since 1931.

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Boston, 10, Chelsea, 1, Dedham, 1, Everett, 2, Revere, 2, Somerville, 1, Westminister, 1, total, 18.

Dysentery, bacillary, was reported from: Salem, 3, Swampscott, 1, Waltham, 3, Worcester, 8, Wrentham, 6; total, 21.

Malaria was reported from: Everett, 1, Haverhill, 1, Lynn, 1, Malden, 1; Worcester, 1, total, 5.

Meningitis, meningococcal, was reported from: Brookfield, 1, Cambridge, 1, Hingham, 1, Montague, 1, Quincy, 1, total, 5.

Meningitis, Pfeiffer bacillus was reported from: Cambridge, 1, Holyoke, 1, Leominster, 1, total, 3.

Meningitis, pneumococcal was reported from: Boston, 1, Cambridge, 1, Everett, 1, Quincy, 1, total, 4.

Meningitis, staphylococcal, was reported from: Chelsea, 1, total, 1.

Meningitis, undetermined, was reported from: Agawam, 1, Chicopee, 1, Haverhill, 1, Holden, 1, Holyoke, 1, Hopedale, 1, Worcester, 1, total, 7.

Poliomyelitis was reported from: Agawam, 1, Brookline, 2, Dighton, 1, Easthampton, 1, Gloucester, 1, Ipswich, 1, Lynnfield, 1, Malden, 1, Newton, 1, Milford, 1, Salem, 2, Somerville, 1, Wrentham, 1, total, 15.

Salmonellosis was reported from: Ipswich, 1, Lynn, 1, Malden, 1, New Bedford, 1, Norwood, 1, Peabody, 1, Worcester, 2, total, 8.

Septic sore throat was reported from: Amesbury, 1, Boston, 4, Cambridge, 1, Greenfield, 1, Montague, 1, Warren, 1, total, 9.

Tetanus was reported from: Great Barrington, 1, total, 1. Triebniosis was reported from: Lawrence, 1, Lenox, 4, Lowell, 1, Pittsfield, 1, total, 7.

Typhoid fever was reported from: Boston, 1, total, 1.

Undulant fever was reported from: Avon, 1; Boston, 1, Dalton, 1, total, 3.

## MISCELLANY

### UNFILLED VACANCIES IN HEALTH DEPARTMENTS

Unfilled professional vacancies in state and local health departments of twelve States, totaling 590 more than in 1945, were disclosed recently when the Committee on Training of Public Health Personnel, United States Public Health Service, Federal Security Agency, announced the results of a spot survey made last spring. The Committee conducted the survey in April, 1947, as a follow-up of a compilation made in July, 1945, when 38 state and 930 local health departments reported a total of 2595 vacancies in nineteen categories of full-time positions and 2000 positions being held for persons in the armed services. Although incomplete information was supplied by eight of the twelve states queried last spring, a total of 1847 unfilled jobs were reported in the same nineteen categories for which the twelve states recorded 1257 vacancies in July, 1945. Replies from these states indicated that the impact of medical men returning from military duty had not yet been felt. In thirteen of the nineteen types of positions, vacancies reported in 1947 were greater than those in July, 1945. Prominent totals among unfilled positions in the twelve States checked last April were health officers, 117 (55 in 1945); medical officers, 186 (101 in 1945); graduate nurses, 940 (654 in 1945), and sanitary and public-health engineers, 81 (36 in 1945). The states included in the spot survey were California, Colorado, Georgia, Illinois, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, New York (exclusive of New York City), North Carolina and Texas.

### ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICERS

At the annual meeting of the Association of State and Territorial Health Officers, held recently in Washington, D. C., the following officers of the Association were elected: president, Dr. Vlado A. Gettung, of Massachusetts; vice-president, Dr. R. L. Cleere, of Colorado, and secretary-treasurer, Dr. L. E. Burney, of Indiana. The Executive Committee members for 1948 include Drs. Gettung and L. E. Burney and Dr. R. R. Cross, of Illinois, Dr. P. E. Blackerby, of Kentucky, and Dr. F. C. Beelman, of Kansas.

### UNITED STATES PUBLIC HEALTH SERVICE RESEARCH FELLOWSHIPS

Research fellowships for the support of research workers in the medical and related sciences have been made available by the United States Public Health Service. Three types of fellowships are awarded. A predoctorate research fellowship, carrying yearly stipends of \$1200 for successful applicants without dependents and \$1600 for those with dependents, in addition to tuition fees, which are paid by the United States Public Health Service, is available to qualified applicants with a Bachelor's degree who wish to conduct research at the Bachelor level and to medical students who, having completed one or two years of medical school, wish to spend additional time in a basic science (such as biochemistry, physiology and physics) before completing their studies toward the M.D. degree. A predoctorate research fellowship, carrying yearly stipends of \$1600 for successful applicants without dependents and \$2000 for those with dependents, in addition to tuition fees, is available to qualified applicants with a Master's degree who wish to conduct research at the Master level and to medical students who, having completed one or two years of medical school, wish to spend additional time in a basic science before completing their studies toward the M.D. degree. A postdoctorate research fellowship, carrying yearly stipends of \$3,000 and \$3,600, respectively, for doctors without and those with dependents, is available to qualified applicants with a Doctor's degree in medical or related fields, an increase of \$300 each year being granted to fellows who are reappointed. And a special research fellowship, which does not carry a set stipend but is determined in the individual case, is available to applicants who qualify

for a postdoctorate fellowship and, in addition have demonstrated outstanding ability or who possess specialized training for a specific problem.

The fellowships are awarded for one-year periods and may be renewed. Except in unusual circumstances, postdoctorate fellows are not reappointed for a third year. Applications are acted upon and awards made at intervals of approximately three months.

Application forms and further information may be obtained from the Division of Research Grants and Fellowships, National Institute of Health, Bethesda 14, Maryland.

## CORRESPONDENCE

### COMMENTS ON FOLIC ACID

*To the Editor* It was with considerable interest that I read your editorial entitled "Folic Acid" in the February 6 issue of the *Journal*. Since at the time I had been using the vitamin for over a year and had no less than 75 patients under treatment, I was especially impressed by your statement that "folic acid as a practical therapeutic agent does not, however, directly provide 'new hope for anemics,'" and that the possible benefit of the "oral therapy" might lead to "neglect of therapy," which is a definite disadvantage.

I have tried, therefore, to restrain myself from the exaggerated optimism and enthusiasm that often accompany the introduction of a new therapeutic agent and have been carefully watching the results with an unprejudiced mind for over two years.

Just now, when our series of sprue patients treated with folic acid is over 100, I have read your second editorial, entitled "A Warning Regarding the Use of Folic Acid," which appeared in the November 6 issue of the *Journal*—the same issue in which Sargent's review, "Folic Acid, Pteroylglutamic acid and related substances," is presented.

Although Sargent finishes his paper with the statement that "because a full clinical trial has not been made, it is too early to venture an opinion on the final place of this nutrient in therapeutics," you end the editorial by stating "Consequently the use of folic acid as a therapeutic agent appears to offer no new benefit but only risk to the patient."

In pernicious anemia, the risk appears to be the alarming incidence of reported neurologic relapses or progression of pre-existing neurologic lesions, sometimes with an explosive onset and spread. Two cases of sprue have been noted by Ross in the United States in which neurologic lesions occurred during folic acid therapy. Of three possible mechanisms of folic acid action on the neurologic disturbances, you mention that the nutrient "may actually exert a positively deleterious influence on the nervous system."

We agree with Sargent that a more exact definition of the clinical entities being studied is essential for the just appreciation of the real effect of therapy. We have seen cases treated for sprue, both here and abroad, that did not fulfill the most important criteria for diagnosis. Two years ago, at one of the clinics of the postgraduate courses sponsored by the American College of Physicians, in a Boston hospital, we were shown the case of an aged woman physician suffering from sprue, who failed to respond to the oral administration of folic acid. The diagnosis was based on steatorrhea and hypochromic anemia.

We have not yet observed the development of neurologic disturbances in sprue during folic acid therapy. The only patient showing typical signs of combined-system disease as pointed out by Suárez, Spies and Suárez ("The Use of Folic Acid," *Ann Int Med* 26:643, 1947) had the condition before the vitamin was started, the question whether it was a case of sprue or of pernicious anemia is still unsettled.

In going over our cases, we can say that the hematologic response of sprue patients to folic acid is as good as that observed with liver extract, but the improvement in their gastrointestinal manifestations is more striking. A number of patients who had been maintained on parenteral liver therapy and were changed to oral folic acid are today—over a year later—in the same, or better, condition than when the change was made.

It is a fact that the response of sprue to folic acid may be facilitated by an accompanying adequate diet, but the same thing holds true of liver extract.



We have yet to see, in this part of the world, any harmful effect that could be attributed to the administration of pteroylglutamic acid

R M SUAREZ, M D

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## BOOK REVIEWS

*Neuropathology in its Clinicopathologic Aspects.* By I Mark Scheinker, M D. With a foreword by Tracy J Putnam M D 8<sup>th</sup> cloth, 306 pp, with 208 illustrations. Springfield, Illinois Charles C Thomas, 1947 \$6.75

This short book on neuropathology emphasizes the more frequent diseases of the nervous system — those likely to be encountered in the practice of medicine. The material is designed for the practitioner, many of the finer details of neuropathology and descriptions of the rarer conditions have been either abbreviated or left out altogether. The diseases considered are presented in an excellent, clear style, the case histories are brief and add to the value of the book in view of its primary aim. The illustrations are well produced although many of them lack the fine details of delineation associated with most books on the subject. The bibliography and index are adequate. In spite of the fact that there are many books available on the subject, this volume should be considered useful in its limited field.

*A Prelude to Modern Science. Being a discussion of the history sources and circumstances of the "Tabulae Anatomicae Sex of Vesalius"* by Charles Singer and C Rabin. Publications of the Wellcome Historical Medical Museum New Series, No 1 F<sup>o</sup> cloth 58 pp with 59 illustrations Cambridge University Press, 1946.

This folio volume dedicated to D Arcy Thompson and Charles Sherrington, is a discussion of the history sources and circumstances of the six anatomic tables of Vesalius first published in 1538, the precursors of his *De Fabrica Corporis Humani* of 1543 and a prelude to all modern science. The authors seek by their study to display some of the forces that converge to make Vesalius a figure of such scientific importance as the father of modern anatomy and some of the currents of sixteenth century thought that enter into his work.

In the *Tabulae* of 1538 renaissance classical scholarship was grafted on medical tradition. Renaissance art was late in influencing anatomy. The *Tabulae* of Vesalius contained the first attempt to represent the vascular system by drawing but graphic anatomy soon destroyed astrologic medicine. The *Tabulae* themselves like incunabula were printed from wood blocks. The first three, drawn by Vesalius himself illustrate the Galenic physiology of the liver and portal system of the liver and venae cavae and of the heart and arterial system. The last three, representing the anterior lateral and posterior aspects of the skeleton with many postural faults were drawn by van Calcar an inferior pupil of Titian.

Born at Brussels in 1514 and educated at Louvain Vesalius went in 1533 to Paris, where Sylvius (Du Bois) had begun teaching in 1531. Estienne though ten years older than Vesalius did not take his medical degree until six years later. Vesalius began to dissect at Paris for Gnanther but returned in 1536 to Louvain where he dissected his first female body and found a corpus luteum and in the same year prepared his first complete skeleton.

In 1537 Vesalius went to Italy where his chief predecessors had been the humanist anatomists Valla of Venice, Benedectus of Padua, Benevienti of Florence and Gerbi and Acheli of Padua and Bologna. The first early Italian illustrated anatomies to appear were those of Berengar of Capri about 1520 and Massa of Venice in 1536.

The authors further describe Galenic physiology and its Latin presentation and discuss certain anatomic elements in the *Tabulae* constituting ideal material for the study of renaissance anatomic vocabulary, which consists of classical and semitic elements in about equal parts. The Hebrew and Arabic influences in anatomic nomenclature are studied in detail particularly the passage of Arabic terminology to the Latin West.

Finally the authors translate into English with learned commentary, the entire Latin text of the *Tabulae*, includ-

ing a discussion of many of the associated Arabic, Greek and Hebrew terms, and at the end of the volume the six *Tabulae* and their accompanying text are reproduced in facsimile reduction to about half diameter. Besides the *Tabulae* this volume is illustrated with fifty nine figures reproduced from various medieval sources and concludes with four indexes respectively in English, Greek Arabic and Hebrew. It is a memorable and monumental work of scholarship and a priceless treasure to all students and teachers of anatomy and of medical history.

*Cineplasty.* By Henry H Keeler, M D, Ph D. With a foreword by Ross T McIntire Vice Admiral (MC), U S N the Surgeon General, United States Navy 8<sup>th</sup>, cloth, 201 pp, with 199 illustrations. Springfield, Illinois Charles C Thomas, 1947 \$6.75

This book is written by the foremost authority and advocate of cineplastic amputations in the United States. He outlines its history and early attempts and then discusses the indications and technique for this procedure in both the upper and the lower portions of the arm. The aftercare and the rehabilitation of the patient are discussed in detail. This is an excellent monograph well written and well illustrated. It should be in the hands of all surgeons who perform amputations.

*Arthritis and Related Conditions.* Edited by Theodore F Bach, M D 8<sup>th</sup>, cloth 472 pp with 139 illustrations Philadelphia F A Davis Company 1947 \$6.50

Bach has attempted to write a concise readable book for the general physician. This book was begun by the late Dr R Garfield Snyder whose contributions have been retained for the most part. The book begins with an excellent résumé of the history of arthritis. Diagnostic aids are then evaluated. Special chapters are contributed by well known men. The book gives a practical concise picture of the various forms of arthritis and their treatment. It is unfortunate that the author uses many old pictures, borrowed from exhibits of the American Rheumatism Association in the early part of the past decade. Many of the other pictures are not clear. More and better pictures would have greatly improved the teaching value of this book. One would prefer to see the usually accepted nomenclature, rather than "atrophic" and "hyper trophic arthritis" used. The book can be recommended as a good review of knowledge, with adequate directions for treatment for the general physician.

*The Engrammes of Psychiatry.* By J C Nielsen M D and George N Thompson, M D 8<sup>th</sup>, cloth, 509 pp with 28 illustrations. Springfield Illinois Charles C Thomas 1947 \$6.75

With this book the authors have provided a new treatise which differs from others because of its basic underlying principles. The volume is a presentation of psychiatric material, seen in the light of neurologic and bioanatomic concepts. It is, as the authors state, "a system of biological psychiatry where the Engrammes — the neuronal patterns of normal and abnormal thoughts and behavior are delineated gathered and systematized." This approach is fully elaborated in the first part, in which the various concepts of consciousness, emotions, perception, recognition and so forth are exposed against a background of neuroanatomic and physiologic knowledge.

The clinical part of the work however is somewhat uneven in some chapters as in the one on schizophrenia, the psychopathology of the disturbance is too briefly surveyed and quite superficially handled. The authors claim not to have had any desire of bringing new theories or new dynamics of interpretation of mental diseases into this book but simply to present all the psychiatric material that can be supported by physiologic explanation. The chapter on psychosomatic medicine seems to be up to date and constitutes a reference that is not found in previous textbooks of this type. The didactic material is interspersed with many clinical cases — most of them personal experiences of the authors — and some of them worth being remembered.

The style is easily phrased and, for this reason under standable by the average student. A good-sized bibliography gives possibility of further reference in many of the topics discussed.



*Deep Analysis The clinical study of an individual case* By Charles Berg, M D (Lond ), D P M 8°, cloth, 254 pp New York W W Norton & Company, Inc, 1947 \$3 50

This book is devoted to the psychoanalytical study of one case. The work is divided into three parts, which are entitled "Part I, Father," "Part II, Mother" and "Part III, Son." In Part I, a glimpse of the technic and method of procedure is given. Transference takes place, and the emergence of a father fixation is also seen in this section. Part II consists of further interviews and the emergence of the mother fixation from beneath the father fixation. In Part III, the subject gains psychologic emancipation, and the author makes a point of stating, "Life has to be lived to be known and the analytical amelioration has to be experienced to be appreciated." How successfully the subject was emancipated after his analysis may be gauged by the author's statement "He [the subject] had inherited life, and life was already in the process of inheriting him."

The patient displayed many interesting symptoms but during free association he made statements that gave the impression that he had read a number of Freud's works. An attempt has been made by documenting these interviews to give the reader insight into the patient's emotional structure and the mechanisms of his psychic patterns. The book, in the reviewer's opinion, is mainly of interest to the psychiatrist engaged in practicing psychoanalytical therapy.

## NOTICES

### HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held on Tuesday, January 13, at the Massachusetts General Hospital. A symposium will be presented by the Department of Psychiatry of Harvard Medical School.

#### PROGRAM

4 45-6 15 p m, in the Bigelow Amphitheater of the White Building

Problems in Psychotherapy Stanley Cobb, M D

Procedures in Psychotherapy Jacob E Finesinger, M D

Some Contributions of Social Sciences Erich Lindemann, M D

6 30 p m Supper, in East Pay Cafeteria, White Building

8 00 p m, in Lower Out-Patient Amphitheater

Studies with Adreno-cortico-trophic Hormone in Psychoneurotic Patients Harley C Shands, M D, Frederick C Bartter, M D, and Gregory Pincus, Sc D

A Study of the Levels of Consciousness in Pentothal Anesthesia Henry W Miles, M D, and John H Tucci, M D

Some Physiologic Mechanisms Underlying the Electrical Activity of the Brain Mary A B Brazier, Ph D, and Jacob E Finesinger, M D

Subsequent meetings will be held on February 10, March 9, April 13 and May 11.

### NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, on Tuesday, January 13, at 8:00 p m. Dr John Hugh Tucci will speak on the subject "Pentothal Narcosis and Succinate."

Physicians and medical students are invited to attend.

### FIRST INTERNATIONAL POLIOMYELITIS CONFERENCE

The National Foundation for Infantile Paralysis has announced that it will sponsor the first International Poliomyelitis Conference at the Waldorf-Astoria Hotel, New York City, from July 12 to 17. The State Department has been

requested to transmit invitations to more than sixty foreign governments to send official delegates to the conference. These officials will be asked to present summarizations of the problems of poliomyelitis in their countries at a special session. The presiding officer at this session will be Thomas Parran, M D, surgeon general of the United States Public Health Service.

The program will include scientific and technical papers on research and treatment of poliomyelitis to be presented by professional authorities in the field from this country and abroad. In addition, there will be panel discussions on the various subjects.

Headquarters have been established in the Waldorf-Astoria Hotel under the direction of Stanley E Henwood, of Chicago, who has been appointed executive secretary of the conference. Arrangements for the conference will be directed from there by Mr Henwood. In addition to the sessions, there will be scientific exhibits, demonstrations of muscle testing and treatment procedures, and a film program.

### MISSISSIPPI VALLEY MEDICAL SOCIETY 1948 ESSAY CONTEST

The Eighth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1948. The society will offer a cash prize of \$100, a gold medal and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the thirteenth annual meeting of the Mississippi Valley Medical Society to be held in Springfield, Illinois, September 29 and 30 and October 1, 1948, the Society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1948. The winning essay in the 1947 contest appears in the January, 1948, issue of the *Mississippi Valley Medical Journal*. Further details may be obtained from Harold Swanberg, M D, Secretary, Mississippi Valley Medical Society, 209-224 W C U Building, Quincy, Illinois.

### AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 6, 1948.

Arrangements will be made, so far as is possible, for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 16-22, 1948, in Washington, D C. Notice of the exact time and place of the Part I and II examinations will be sent all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M D, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

### POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY

The Association for the Study of Internal Secretions announces a Postgraduate Assembly in Endocrinology to be held in Los Angeles from February 23 to 28. Applications should be sent to Dr E Kost Shelton, chairman, Committee on Postgraduate Instruction, 921 Westwood Boulevard, Los Angeles 24, California.

(Notices continued on page xi)

## NOTICES (Continued from page 36)

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 8

## FRIDAY JANUARY 9

- \*9:00-10:00 a.m. Carcinoma of the Prostate Dr. George G. Smith, Joseph H. Pratt Diagnostic Hospital  
 \*10:00 a.m.-12:00 p.m. Medical Staff Rounds Peter Bent Brigham Hospital  
 12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital) Joseph H. Pratt Diagnostic Hospital

## MONDAY JANUARY 12

- 12:00 m. Clinicopathological Conference Margaret Jewett Hall Mt. Auburn Hospital Cambridge.  
 \*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital

## TUESDAY JANUARY 13

- \*12:15-1:15 p.m. Clinicorontogenological Conference Peter Bent Brigham Hospital  
 4:45 p.m. Harvard Medical Society Massachusetts General Hospital  
 \*8:00 p.m. New England Society of Anesthesiologists. Bigelow Amphitheater of the White Building Massachusetts General Hospital.

## WEDNESDAY JANUARY 14

- \*9:00-10:00 a.m. Pediatric Clinicopathological Conference Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital  
 \*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
 \*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater Children's Hospital

\*Open to the medical profession

JANUARY-APRIL Thirteenth Postgraduate Seminar in Neurology and Psychiatry Metropolitan State Hospital Page 348 issue of August 28  
 JANUARY 7 Theta Alpha Omega Alpha Page 1004 issue of December 25  
 JANUARY 8 New England Hospital for Women and Children. Page 1004 issue of December 25

JANUARY 8 Dysmenorrhea Dr. Joe V. Meigs Pentucket Association of Physicians, 8:30 p.m. Haverhill

JANUARY 13 New England Society of Anesthesiologists. Page 36

JANUARY 13 Harvard Medical Society Page 36

JANUARY 14 Phi Delta Epsilon Lecture. Page 968 issue of December 18.

JANUARY 20 and 21 American College of Surgeons. Commodore Perry Hotel Toledo Ohio. Page 910 issue of December 11

JANUARY 26 AND 27 American College of Surgeons. Ansley Hotel Atlanta Georgia. Page 910 issue of December 11

JANUARY 30 AND 31 American College of Surgeons. Oklahoma Biltmore Hotel Oklahoma City Page 910 issue of December 11

JANUARY 30 AND 31 Conference on Normal and Pathologic Physiology of Pregnancy. 1004 issue of December 25

FEBRUARY 6 American Board of Obstetrics and Gynecology Page 36

FEBRUARY 23-28. Postgraduate Assembly in Endocrinology Page 36

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc. and American Association of Industrial Dentists Hotel Statler Boston

APRIL 19-23 American College of Physicians. Page xiii, issue of July 31.

MAY 6-8. American Association for the Study of Gout. Page xiii issue of July 31

MAY 17-20 American Urological Association. Hotel Statler Boston

MAY 18-22 American Association on Mental Deficiency Copley Plaza Hotel, Boston.

MAY 25-27 Massachusetts Medical Society Annual Meeting. Hotel Statler Boston

JULY 12-17 First International Polymyositis Conference. Page 36

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

JANUARY 13

MARCH 9

May 11 Annual Meeting Hotel Walden.

All other meetings will be held at the Franklin County Hospital.

## MIDDLESEX EAST

JANUARY 21

MARCH 24

MAY 12. Annual Meeting.

All meetings will be held at the Bear Hill Golf Club.

## NORFOLK

JANUARY 27 Round Table Discussion: Bleeding from the alimentary tract.

FEBRUARY 24 Obstetric and Gynecologic Night

MARCH 23 Harvard Night.

## PLYMOUTH

JANUARY 15 Brockton Hospital Brockton

FEBRUARY 19 Toll House Whitman

MARCH 18. Goddard Hospital Brockton

APRIL 15 State Farm Bridgewater

MAY 20. Lakeville Sanatorium, Lakeville

## WORCESTER

JANUARY 14 St Vincent's Hospital

FEBRUARY 11 Worcester State Hospital.

MARCH 10 Memorial Hospital

APRIL 14 Hahnemann Hospital

MAY 12 Annual Meeting

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New Eng J Med., 234-783 1946

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Rachitic changes were present as late as the fourteenth year, and the incidence was higher among children dying from acute disease than in those dying of chronic disease.

The authors conclude, "We doubt if slight degrees of rickets, such as we found in many of our children, interfere with health and development, but our studies as a whole afford reason to prolong administration of vitamin D to the age limit of our study, the fourteenth year, and especially indicate the necessity to suspect and to take the necessary measures to guard against rickets in sick children."

\*R H Follis, D. Jackson, M. M. Eliot, and E A Park Prevalence of rickets in children between two and fourteen years of age, Am J Dis. Child 66 1-11, July 1943.

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## CERTAIN PUBLIC-HEALTH ASPECTS OF INFECTIOUS DISEASES

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NEW YORK CITY

THERE are at least two ways of viewing infectious diseases, the first is from the standpoint of the individual, and the second is from the standpoint of the community. Curative and preventive medicine usually deals with diseases in individual patients, whereas the handling of them in a community and in relation to environmental factors comes within the realm of public health. In general, each infectious disease shows a characteristic pathogenesis in individual patients, and it is the duty of physicians to have knowledge of this and of how to handle the situation for the benefit of the patients. It is equally true that each infectious disease presents a characteristic pathogenesis in a crowd or in a community, and it is the duty of health officers to know about it and about ways and means of meeting the situation for the benefit of the community. Frequently, it is difficult to determine the point at which the practice of medicine stops and the duties of the health officer begin, many arguments are now in progress concerning this matter. I have no desire to take part in them, for most of them are footless. In passing, however, I should like to register my agreement with Dean Clark's statement "It is safe to say that at least three-fourths of the preventive work made possible by present-day medical science must be carried by the practising physician." The following remarks are limited to certain public-health aspects of infectious diseases, and emphasis is placed on ecologic phenomena.

Dr. Hermann M. Biggs, who died in 1923 and who is considered by most workers to have been one of the greatest figures, if not the greatest, in the history of American public health, made the remark that public health is purchasable, this subject is discussed in greater detail below. The features of infectious diseases that interest workers in the public-health field are their origin, entry into and spread within a community and their control at a community level. Ideas and methods of handling infectious diseases at times undergo rapid and drastic changes. In fact, revolutionary ideas may occur within the lifetime of a single person. This happened to Biggs, who while a candidate for the degree of Bachelor of Arts

at Cornell obtained a leave of absence for a few months to study at Bellevue Hospital Medical College. The influence of that experience is reflected in his baccalaureate thesis, "Sanitary Regulations and the Duty of the State in Regard to Public Hygiene." For the most part, statements in his thesis hold today as well as they did in 1882. However, the accuracy of one remark would be questioned at the present time, in fact, Biggs himself later did much work to show that such a statement was inaccurate. The section referred to is as follows:

It is now universally acknowledged by all medical authorities that a number of these diseases such as cholera, typhoid fever and diphtheria may be generated *de novo* in certain localities from the use of impure water and the existence of unsanitary conditions, and thence are scattered by contagion. And it is now believed by some of the best medical writers that many if not all of the remainder of these diseases such as smallpox, scarlet fever and measles were originally among the so-called filth diseases, and originated from essentially the same conditions as the others. If this is true we are forced to the conclusion that all of these zymotic diseases the most terrible known to man, that have wrought so much misery, desolation and death in the world are the direct results of man's own carelessness and negligence, the inevitable penalty of the violation of sanitary laws.<sup>1</sup>

In 1885, after Biggs had obtained his medical degree, he and Breneman made a similar statement during the investigation of an epidemic of typhoid fever in Plymouth, Pennsylvania:

If it be possible for typhoid fever to originate *de novo* in filthy surroundings and in the use of polluted water, no more remote point need be looked for as a starting point of the disease which spread from a single patient in this house to hundreds in the village. Every thing points therefore to the conclusion that the disease which spread from this house also originated there.<sup>2</sup>

Before Biggs died it had generally been accepted that bacteria and other infectious agents do not arise *de novo* or spontaneously and that diseases caused by them result only from the entrance of such agents into a host. At the time of his death, the present activity in the study of virus diseases had begun but was not far advanced. If he had lived longer, it is obvious, in view of his early statements regarding the spontaneous origin of certain maladies, that he would have been greatly interested in the

\*Director, Hospital of the Rockefeller Institute for Medical Research.

present-day discussions of the origin and nature of viruses

Since the discovery of the first filterable virus in 1892, innumerable observations concerning the nature of these active agents have appeared. The outstanding work of Stanley<sup>3</sup> in 1935, which resulted in the crystallization of tobacco mosaic virus, has precipitated another epidemic of discussions, many of which are reminiscent of older arguments concerning the spontaneous origin of mice, worms, flies, bees and bacteria. In fact, a few workers within the last twenty years have contended that they have experimentally produced viruses from normal bacteria or from normal mammalian tissues. None of these experiments have been confirmed or generally accepted. At least most of us account for positive results on the basis of the presence of latent, unrecognized viruses in the so-called "normal tissues" or other biologic materials used in the experiments.

### NATURE OF VIRUSES

The demonstration that certain plant viruses are crystalline nucleoproteins has left a deep impression upon the scientific world in general and upon the chemists in particular who take the attitude that all viruses are crystalline nucleoproteins. Of course this is not true, but it is difficult to get certain people to believe that it is not. Viruses are not all alike, and they vary greatly in complexity. Some of them are very complex—for instance, the elementary bodies of vaccinia, which have been thoroughly studied, approach the size and complexity of small bacteria. The one characteristic common to all viruses is that they are obligate parasites in the sense that no one has ever induced them to multiply outside a living susceptible host cell.

As a result of recent discussions on the origin and nature of viruses, I have heard it asked "What is the use of attempting to prevent the spread of virus diseases if viruses are fabricated by their hosts?" Physicians, public-health officers and others interested in public-health problems should not become alarmed or misled by such questions or statements. In spite of a few unsubstantiated claims to the contrary, no case of a virus disease arising spontaneously in a patient has been established. Indeed, all the evidence points to the fact that virus diseases, regardless of the nature of the active agents inducing them, will act in the future as they have in the past—that is, a patient who comes down with a virus ailment will do so because, in some manner, he contracted the infection from without rather than through its spontaneous fabrication within. In other words, when one is developing plans for the control of virus maladies, there is as yet no reason to alter current ideas regarding the importance of obligate communicability in the origin and spread of virus infections.

In view of what has been said, it remains to explain why certain virus diseases of human beings have appeared on the horizon within the last twenty

to twenty-five years. This applies particularly to recently discovered virus diseases that attack the central nervous system of man. An obvious answer is that at least some of them had been present for a long time and were not recognized because of the lack of adequate technics. In spite of this obvious answer, it is still strange that St. Louis encephalitis suddenly appeared in 1933 and has not been traced back any farther than to a small outbreak, which occurred in Paris, Illinois, in 1932. Although another epidemic appeared in St. Louis in 1937 and the disease is known to occur sporadically in certain Western States, it has never caused any trouble on the Eastern seaboard. This disease leaves neutralizing antibodies in the blood of patients who recover. Therefore, it is possible to say that human beings in certain parts of the world have not as yet been infected by this virus. Where the virus was before it attacked human beings in 1932 and 1933 is not known. This is a peculiar situation, and there is no adequate explanation for what has occurred. However, one is permitted to speculate concerning the matter, and there are data that enable one to speculate with some hope of arriving at a true answer.

It is characteristic of many viruses to undergo certain changes similar in some respects to those resulting from mutation. Also, a number of viruses possess the ability of adapting themselves to different hosts. Within recent years, seven or eight new viruses have been recovered from wild mosquitoes caught in nature. Most of these viruses are able to attack the central nervous system of experimental animals and to produce encephalitis. There is also evidence that some of the viruses have infected human beings without producing recognizable disease. The evidence for this is the presence of neutralizing antibodies in the blood of certain people living in the areas where the viruses were discovered in mosquitoes. It is conceivable that through mutation, adaptation or change in environment certain viruses, which parasitize only mosquitoes and lower animals, suddenly acquire the ability of producing encephalitis in human beings. Certainly this explanation for the appearance of St. Louis encephalitis is more plausible than one based on the spontaneous fabrication of encephalitic viruses in human beings. Such a statement must not be interpreted as a denial of the spontaneous origin of infectious diseases in the past or of its possibility in the future. However, one can safely say that nobody has yet established the spontaneous origin of a single infectious disease and that regarding such diseases the law of obligate communicability still prevails.

### INFECTIOUS DISEASES IN THE COMMUNITY

#### *Etiology*

Infectious diseases are caused by protozoa, fungi, bacteria, spirochetes, rickettsiae and viruses. These agents are endowed with life. All living things have

an ecology and those producing disease are no exceptions. Some of the viruses may not be alive, and yet their ecology, if the word may be used in this context, is so similar to that of living things that they may, for the purpose of this discussion, be considered collectively with other infectious agents. The behavior of infectious diseases in a population is nothing more than an expression of conflicts between various forms of life in an effort to arrive at a satisfactory equilibrium.

Studies of epidemics have been going on for centuries and have been fruitful. Only recently, however, have such investigations been brought within laboratory walls so that controlled experiments of certain types could be performed. Most of the work has been done by Topley and Greenwood in England and Webster and his associates in America. It has been conducted on mice as the experimental host and *Salmonella enteritidis* (*Bacillus enteritidis*), *S. aertrycke* (*B. aertrycke*) and the virus of ectromelia as the infectious agents.

A brief account of how those experiments were performed and a statement of the results will simplify the rest of this discussion. If 100 mice, all of which are free from *S. enteritidis*, are placed in a cage of such size that they are considered to be living under crowded conditions, the animals will get along fairly well. However, if several mice infected with *S. enteritidis* are placed in the cage, infection will spread to the healthy mice, and an epidemic will occur. Many of the animals will die and the epidemic will finally come to an end, but the infection will not disappear entirely from the remaining population; it will smoulder along, and an occasional mouse will die. At this stage, the disease is usually spoken of as being endemic. If at this point in an experiment several healthy mice are added to the cage daily, after a number of days a new epidemic will occur involving the healthy mice in addition to some of those that have passed through the preceding epidemic. If the addition of mice is stopped, the epidemic will subside again, but if the daily addition of a sufficient number of mice is continued, the epidemic will also continue more or less indefinitely. Once such a population of mice becomes seeded with infection, it is very difficult to eradicate it. Topley and his co-workers have attempted to inhibit the occurrence of epidemics by vaccination of mice before addition to the colony. According to them it is impossible in this manner to prevent epidemics completely.

It might be profitable to examine briefly the biological aspects of the observations described above. *S. enteritidis* is a parasitic organism that has difficulty in maintaining itself free in nature; it is more or less dependent upon some host for its continued existence. The experimental epidemics described resulted from a conflict between infectious organisms and hosts. Had *S. enteritidis* killed all the mice, its continued existence would not have been possible. Eventually, a stabilization of infection was effected,

at either the endemic or the epidemic level, depending upon the conditions under which the experiments were conducted. Only in this way could the infecting agent and the host have continued to live together.

Frequently, military-training camps have unwittingly been set up and run in a manner that duplicated the experiments in mice described above. Many healthy men were brought together from different parts of the country, and after a time these populations became seeded with pathogenic organisms, whereupon occasional cases of infection began to appear. Then, several times a week for long periods, groups of new, susceptible men were added to the populations in the camps. As should have been expected, epidemics occurred, and in some camps the incidence of certain diseases remained at epidemic levels for many months. This was particularly true of some respiratory diseases, as best exemplified by hemolytic streptococcus infections.

The experiments in mice, which present a relatively simple picture of how infectious agents act in a crowd, represent in a general way what takes place in most epidemic diseases of human populations. In each instance, hosts and infecting agents strive to keep for themselves a place in the world. The conflicts seesaw back and forth over long periods with epidemics separated by more or less quiet endemic periods. In many instances, neither the host nor the invading agent attains complete supremacy, and eventually some kind of truce is called or an equilibrium is reached. An ideal situation would be one in which both the infectious agent and host could survive without much harm to either. Theobald Smith<sup>4</sup> often referred to ideal parasites, which, according to him, are infectious agents that live peaceably with their hosts. In other words, they infect and immunize their hosts without causing much damage while preserving for themselves a safe place in nature.

In certain instances, equilibriums between human populations and infecting agents have been attained but, for many reasons, have been maintained with difficulty. The rapid addition of susceptible persons through birth or immigration to a population in equilibrium with a pathogenic agent sooner or later results in an epidemic. This is best exemplified by measles, which occurs every two or three years in large cities. There are many other ways in which equilibriums can be upset. Many of these are present during periods of war, when large groups of human beings are dislocated and sanitary conditions and standards of living are poor. The changes that occur under such conditions are more comprehensible than the other variations that have been noted in the behavior of certain epidemic diseases. For example, scarlet fever at present is extremely mild in certain parts of the world, but forty or fifty years ago it was a scourge; there had previously been another period when the disease was relatively mild. Such cycles

in several other diseases have been noted, but no one has adequately explained the phenomenon

### *Transmission*

In general, there are three ways in which infectious agents get from a sick person or carrier to a healthy, susceptible person by droplet infection, droplet nuclei or contact in respiratory diseases such as measles, influenza and scarlet fever, by means of contaminated water, milk or food or by contact in enteric diseases such as typhoid fever, bacillary dysentery and amebic dysentery, and by means of vectors — for example, mosquitoes in malaria and lice in epidemic typhus. Chapin<sup>5</sup> stressed contact infection, more recently, this mode of spread of infection has not been considered very seriously in many diseases, particularly those in which the infectious agent is found in the feces, such as poliomyelitis, infectious hepatitis and dysentery. My experience with hookworm on Guam impressed me with the fact that most of us and our clothes are at times dangerously contaminated with fecal material. For example, a young infant infected with hookworm was placed on a small cotton blanket for twenty-four hours. At the end of that time examination revealed no obvious fecal contamination, and yet when the blanket was moistened and allowed to stand for five days, 20,000 infective hookworm larvae were obtained.

So far, I have discussed situations in which the relation between the infecting agent and the host has been a direct one and in which the maintenance of disease has involved the ecology of only the infecting agent and the host. The diseases spread by the first two methods mentioned are of this kind. Those spread by vectors are ecologically more complex, because, in addition to the ecology of the host and parasite, that of a vector and at times an intermediate host must be considered. A knowledge of these additional factors is essential for the understanding and control of such epidemic diseases as malaria and murine typhus. Thus, for malaria to flourish in a locality, a sufficient density of *Anopheles* mosquitoes capable of transmitting plasmodia is essential. This means that the mosquitoes must be able to find suitable living and breeding places and to protect themselves against natural enemies. This is an ecologic problem so far as a mosquito is concerned. Likewise, if murine typhus is to be established and maintained in a community, there must be a sufficient number of rats to act as reservoirs for the rickettsiae and the proper kind of fleas to transmit them from rats to human beings. Thus, the maintenance of murine typhus in a community and its behavior in regard to endemicity and epidemicity depend upon the ecology of human beings, rickettsiae, rats and fleas.

### *Prevention and Control*

The most common methods of prevention and control of infectious diseases in human populations are

as follows: quarantine, protection of food, milk and water and other aspects of general sanitation, the eradication or control of vectors, reservoirs and intermediate hosts, and vaccination. In dealing with certain animal and plant diseases more drastic measures have at times been employed — for example, the ruthless destruction of all susceptible hosts within a prescribed area.

So far as many diseases are concerned, the world has just passed through a very interesting period. Certain of them unexpectedly gave trouble, whereas others that had been greatly feared remained in the background. Many procedures for the control of a variety of diseases were instituted, some of which have been publicized as having been very successful, in others much faith was reposed in spite of the fact that there was inadequate evidence to justify such an attitude.

In World War I, epidemics of measles complicated by pneumonia presented serious problems for the United States Army. Most men reared in urban communities had had the disease by the time they joined the military forces, whereas many of those from rural districts had never experienced measles. The epidemics occurred in the susceptible soldiers from rural communities. Between World War I and World War II, good roads and numerous automobiles made much of the United States, so far as measles is concerned, urban in character. Consequently, most of the men who joined the Army or the Navy during the last conflict had had measles prior to their enlistment, and this disease, as predicted by some, was of minor importance.

In World War I, influenza was a major scourge and swept the whole world, killing many millions of people. When World War II broke out, investigators predicted that another pandemic of influenza would sweep everything before it. This did not occur, and influenza proved to be of relatively minor importance. Between the two wars, it was shown that influenza can be caused by at least two agents: influenza A virus and influenza B virus. Furthermore, a vaccine capable of protecting approximately 75 per cent of those receiving it has been perfected and was given to certain military personnel. Even the most ardent advocates of influenza vaccines admit that the prevention of a pandemic during World War II did not depend upon their use. In fact, most workers are reluctant to venture an explanation of what happened. Perhaps I shall be forgiven for suggesting one. Between the two World Wars, rapid transportation of all kinds developed by leaps and bounds, making the world one community so far as influenza is concerned. It has been demonstrated that the two known influenza viruses from time to time produce mild or moderate epidemics here and there throughout the world. In view of this, all populations of the world are probably thoroughly seeded with the two viruses, and something similar to a truce has been declared between them and

human beings. If this is true, we shall continue to have mild and moderate epidemics of influenza but never another pandemic similar to the one experienced in 1918, unless a variant, to which a large proportion of the people in the world are susceptible, suddenly originates from one of the two known influenza viruses.

Unlike measles and influenza, which belong to the respiratory group of diseases and are spread by droplet infection, droplet nuclei and contact, typhoid and paratyphoid fever are members of the enteric group and are usually transmitted by means of infected water, food or milk and by contact. These diseases have played a prominent part in most wars. In the United States Army, however, they were of minor importance in both wars. Compulsory vaccination against typhoid and paratyphoid fever was enforced in the American Army during these wars, and many observers attribute their absence to this procedure. There are still a few workers who believe that typhoid vaccination is of no value. The truth probably lies between these two opinions. It must be remembered that enteric diseases in many countries were well on the way to being controlled long before the use of vaccines. In fact, considerable progress had been made in the control of typhoid fever in England before the discovery of the typhoid bacillus. The control measures consisted of protecting food, milk and water from contamination by enteric bacteria. At the time vaccination was introduced in the American military forces, better sanitation was also provided for the men, even under fighting conditions. In spite of a few contrary opinions, it is hard for me, because of my experience in the Pacific area, to believe that typhoid vaccination as practiced in the American military forces is without value. Nevertheless, from certain things that happened in the Pacific area and in Europe, it is obvious that vaccination in the absence of proper sanitation will not give complete protection against the disease. Members of United States Naval Medical Research Unit No. 2 had an opportunity to study typhoid and paratyphoid fever in troops that took part in the fighting on Okinawa. In all cases studied the men had been adequately vaccinated or re-vaccinated within a year of the time that they became ill. There can be no doubt of the diagnoses. Some of the infections were severe, but most of them either were mild or had been altered in some way. On questioning, practically all the infected men gave a history of having eaten raw vegetables gathered during combat from native fields that had been heavily fertilized with human feces. These men had obviously become infected even though they had been vaccinated. On the other hand, inspection of the natives and their habits forces the conclusion that many more soldiers would have contracted typhoid or paratyphoid fever had they not been vaccinated. I have been told on good authority that American men detained in some of the German

prison camps, where proper sanitation was lacking, suffered from typhoid and paratyphoid fever in spite of having been adequately vaccinated. In a civilian population, enteric infections should be controlled through proper sanitary measures and personal habits. In time of war, particularly in the fighting forces, it may not be possible always to maintain proper sanitation and control of personal habits. Under such conditions, vaccination should be employed, but it must be remembered that even in the armed forces sanitation cannot be disregarded if enteric diseases are to be kept in a position of minor importance.

Each year, malaria is responsible for more sickness and deaths throughout the world than any other disease. The American forces expected malaria in the South Pacific area, but the early handling of the malarial problem in that area was not brilliant. Defects, however, were rapidly rectified, and the problem in the latter part of the Pacific struggle was handled better. When the war ended quinine (Atabrine) was still being used for the suppression of the disease. This drug does not prevent infection. Great efforts were made in America and in England to find true prophylactic and curative agents, both countries believe that they have made progress toward this goal. It will be interesting to observe what the new drugs will do toward controlling or eradicating malaria.

Before World War II, great strides had been made in the control of mosquitoes by means of oil, Paris green and freon-pyrethrum mixtures. During the war, DDT was added to the list of insecticides of value for use against Anopheline larvae and adults. The occurrence and persistence of malaria among human beings depend upon the ecology of Anopheline mosquitoes, of which there are many kinds, each one has an ecology of its own. Methods of controlling or eradicating one kind do not necessarily apply to another. Anopheline mosquitoes are not found on certain islands in the Pacific area, and great efforts have recently been made in many directions to prevent their introduction. Much has been said about the success of these efforts. Having spent some time in the South Pacific and Central Pacific areas and having seen how control measures were carried out, I wonder whether they had much to do with the successes mentioned. In any event, these areas remained free for centuries before institution of the control measures. Therefore, I suspect that there is some ecologic reason why Anopheline mosquitoes find it impossible or difficult to establish themselves in one of the areas. Attempts should be made to establish Anopheline mosquitoes on a small, unimportant island. If the results of the experiment were negative, desirable information would have been obtained, if they were positive, it should not be difficult to eradicate the mosquitoes.

I have discussed this matter with a number of people, who usually show little enthusiasm for the



idea that it would be difficult to establish Anopheline mosquitoes on Pacific islands now free from them. They point to the fact that *Anopheles gambiae* was taken from Africa and established in Brazil, an entirely new habitat. They also point out that this mosquito recently spread up the Nile into a territory where it had not previously been found. It is admitted that some Anopheline mosquitoes can establish themselves in new homes, but it must be remembered that others had already found suitable habitats in Brazil and Egypt before *Anopheles gambiae* joined them. Consequently, I do not believe that anyone should state that Anopheline mosquitoes can establish themselves on certain islands in the Pacific area merely because *Anopheles gambiae* was able to find new homes for itself in Brazil and Egypt.

In speaking of recent advances in the fight against malaria, one writer has made the following statement: "But the most important lesson is that malaria can be controlled anywhere in the world, in any environment, when trained and organized personnel are given the necessary supplies and authority."<sup>6</sup> It is true that much can be done in the control of many Anopheline mosquitoes, but the eradication of a species is very difficult. It is an established fact that *Anopheles gambiae* was eradicated from Brazil and Egypt, but it is also a fact that other Anopheline mosquitoes in Brazil and Egypt were not eradicated at the same time. It has been suggested that a recently implanted species might be more easily eradicated than one that had been established for centuries in an area. Thus, one might doubt whether it would be possible or practicable at present to eradicate *Anopheles gambiae* from its well established African home. At least, an effort should be made to ascertain how difficult it is to eradicate Anopheline mosquitoes from a long-established stronghold. The island of Sardinia has been mentioned as a place where such work might be done with profit.

Polio myelitis came into prominence a little more than a century ago, although it had undoubtedly been present in various parts of the world for a long time. The virus has been found in the nasopharyngeal secretions and feces of patients and contacts. It has also been demonstrated in sewage of communities in which the disease was active and in flies collected in such communities. Since the virus is in feces and since it is admitted that a virus entering the mouth can infect a human being, it is obvious that contaminated water, milk and food can at times lead to outbreaks of the disease. In fact, several epidemics caused by contaminated milk have been reported. In spite of this, most workers in the field believe that the mechanism described above is not necessary for the usual spread of the virus in a population.

As a rule, epidemics of polio myelitis are not explosive. The disease appears to spread radially from

a given point or area, the cases becoming fewer as the distance from the center of the area increases. Furthermore, once someone in a family becomes infected, the family frequently acts as an epidemiologic unit. This type of transmission is not characteristic of diseases usually disseminated through water and milk and is more like those that are spread by droplet infection, droplet nuclei and contact. Since more viruses are found and persist in feces for much longer periods than in the nasopharyngeal secretions, most workers in this field are inclined to believe that through contact of various kinds the virus in the feces of an infected person is transported to the mouths of susceptible people.

As stated above, polio myelitis became epidemic a little more than a century ago and was noted at that time in certain parts of Europe. It did not become very obvious in the United States until the latter part of the last century, since when it seems to have been increasing in prevalence. It is believed that this is a real increase in the number of obvious cases and is not to be explained by more frequent diagnosis. During this period in the United States many infectious diseases, particularly those due to poor sanitary conditions, have decreased in prevalence. This seems to be a paradox: the cleaner the country becomes, the more cases of polio myelitis occur.

It is known that the virus of polio myelitis can induce inapparent infections and a mild disease without paralysis as well as a paralytic disease. In fact, there are only a few paralytic cases in comparison to the other kinds. There are neutralizing antibodies against the virus in 85 to 90 per cent of the adult population tested in the United States. In Africa (particularly in Egypt), China and Japan, it has been shown that at least 85 to 90 per cent of the adult population possess neutralizing antibodies against the virus. In spite of the fact that most adults of these countries possess neutralizing antibodies, very few cases of paralytic polio myelitis are seen. As is well known, the sanitary conditions are very poor, and the countries are densely populated—a condition enhancing the likelihood of the spread of a disease by contact.

Paralytic polio myelitis is very rare in young infants, particularly in those under six months of age. It is also known that antibodies against this disease are transmitted from an immune mother to her infant. These antibodies, like those against other infectious diseases, disappear within six to twelve months after birth. If the virus in Egypt, China and Japan is widely distributed and most infants born in those countries are likely to come in contact with the virus one or more times during the early months of life when they are partially protected by antibodies obtained from their mothers, the infants could, through mild unrecognized infections, develop an active immunity that would protect them from a paralytic attack of the disease in childhood.

or adult life. Thus, if the circumstances described are true, the populations of Egypt, China and Japan have arrived at a truce with the virus of poliomyelitis. In other words, the people and virus live happily together. If the equilibrium that now exists were upset by a marked decrease in the density of the population or by the institution of sanitary conditions equal to those in the United States, it is conceivable that a sufficient number of infants would not become actively immunized early in life and that epidemics of paralytic poliomyelitis would make their appearance.

Public-health officials will probably take exception to some of the ideas set forth concerning poliomyelitis. Nevertheless, the likes and dislikes of public-health officials cannot change ecologic laws, and in the control of diseases many things must be kept in mind. If a population is in happy equilibrium with an infectious agent, it may not always be advisable to disturb this equilibrium unless the disease can be eradicated, unless adequate methods for prevention of its re-entry into the population are available or unless an adequate method is at hand for its control upon re-entry.

At present there is no means of controlling the spread of poliomyelitis, and there is no vaccine available for its prevention. If the disease is transmitted by contact or if it is air borne, public-health officials cannot, through the passage of sanitary regulations, break the chain of events sufficiently to stop the spread of the disease, because legislation against human contacts and against breathing are not acceptable. It is true that personal habits can be improved through education, and many experiments are under way in which, through ultraviolet irradiation or aerosols, attempts are being made to sterilize the air. The experiments are interesting, but it is not likely that sterile air will be universally available for a long time.

Quarantine, which is the detention in isolation of contacts and patients with diseases, has been one of the measures employed in the past to prevent dissemination of infectious maladies within a country or from one country to another. Much faith has been placed in this method, but most experienced health officers and epidemiologists are well aware of the fact that quarantine as applied to human diseases, because human nature will never permit it to be sufficiently stringent, offers no great barrier to their spread. In many places, for psychologic reasons if not from ignorance, outmoded quarantine is still in effect, resulting in the waste of much time and money. So far as I know, no epidemic of measles, chicken pox, influenza, poliomyelitis, smallpox and so forth has ever been adequately controlled by means of quarantine. The Board of Health of the City of New York is gradually making isolation or quarantine regulations less and less burdensome to its citizens. At present the regulations are very

mild and simple, and it looks as though many of them will soon be dispensed with entirely.

Since 1815 a number of pandemics of cholera have occurred. Indeed, the disease has been known to spread to many parts of the United States. At times quarantine measures were very strict. Did they do any good? I doubt it. In any event, Greenwood<sup>7</sup> has made the following observations concerning the value of quarantine measures in controlling this disease:

As seems so often to be my fate I must end on a note of interrogation. Why did the Indian variety of cholera acquire a dispersive power a little more than a century ago? Why did it ravage Europe for more than a generation and then lose interest in us? Without going the whole way with Stucker I am prepared to go some distance and to doubt whether the decisions of national and international committees or the blockading of land or sea frontiers have played a much more important rôle than the fly on the wheel.

There is a definite relation between the prevalence and persistence of certain diseases and the sanitary conditions and standards of living. The best way for a country to prevent the entrance and spread of such diseases is to have a civilization and a standard of living that provide poor ecologic conditions for the infectious agents, their vectors and reservoirs. For example, it is not necessary at present to worry about the introduction of cholera and epidemic typhus into the United States, because they would find unfavorable conditions for their establishment and spread.

The statement of Biggs, mentioned above, that public health is purchasable is true within certain limits, one of which is that it cannot be brought alone, there are tie-in purchases, such as the proper kind of civilization and standard of living. Moreover, I strongly suspect that more than one such tie-in purchase has been largely, if not entirely, responsible for specific gains in public-health progress.

Early in the history of this country, malaria was rampant in the Mohawk Valley. It is doubtful whether conscious efforts to do away with Anopheles mosquitoes in that area accomplished much, but, as the fertile land was brought under cultivation, the area became more and more densely populated, with the consequent removal of breeding places for the mosquitoes. Thus, with the advance of civilization, malaria-bearing mosquitoes found ecologic conditions unfavorable for them, and malaria disappeared from the area without any conscious efforts on the part of the inhabitants.

The death rate from tuberculosis in the United States has been decreasing rapidly. Public-health officials and public-spirited organizations have been active, and there is a tendency on their part to ascribe the decrease to their activities. Similar claims have been made regarding many other infectious diseases, as exemplified by the following statement by Grant<sup>8</sup>:

The achievement of health departments in controlling sanitation of the environment and the incidence of communicable diseases with the consequent improvement in mortality rates has already resulted in the well known marked shifts in the age distribution of population and has disclosed the three major lags in medical care, namely, rehabilitation, chronic illness, and mental care.

While health officers and different organizations have been active, many things not directed by them have been happening in the population, and these happenings probably would have occurred in spite of anything that could have been done. I have no quarrel with health officers or with people working in the tuberculosis field, for they have done a good job, but I seriously doubt whether the decrease in incidence of certain infectious diseases and the marked decrease in the death rate from tuberculosis in particular are largely due to their activities instead of resulting from multiple events in the popu-

lation about which too little is known and over which no one has a great deal of control. Undoubtedly, many of these happenings are in some way related to or controlled by ecologic laws  
York Avenue and 66th Street

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## "FEVER OF UNKNOWN ORIGIN" DUE TO LYMPHOGRANULOMA VENEREUM\*

### Report of a Case with Diagnosis by the Use of Quantitative Complement-Fixation Tests

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**L**YMPHOGRANULOMA venereum infection is a localized suppurative process involving the inguinal, femoral and pelvic lymph nodes and the rectum. Although systemic symptoms are common in this disease, prolonged fever is rare. This infection is therefore not usually thought of in the differential diagnoses of febrile conditions. Fever, sweats, headache, tachycardia or relative bradycardia, joint and muscle pains, malaise and anorexia are frequent but, as a rule, cause little concern to the patient. Some cases, however, are so severe that the lymphadenitis appears to be of minor importance in the face of a generalized infection. When generalized symptoms predominate and the tell-tale lymphadenitis is not present, the diagnostic problem presented is no less formidable than the solution of a "fever of unknown origin." In this task, the standard laboratory procedures are of little help.

Recently, such a problem was encountered at the Station Hospital, Camp Lee, Virginia, and its final solution was achieved only through the use of a simple laboratory test that has heretofore had little clinical use—the quantitative complement-fixation test.

#### CASE REPORT

A 33-year-old Negro soldier was first seen at a dispensary on the morning of June 26, 1946, complaining of chills and fever, which had started the night before after an episode of vomiting. He was referred to the hospital and while on the way there he experienced another shaking chill.

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Physical examination was negative except for a temperature of 103.4°F, a pulse of 104, and respirations of 24. A smear for malarial parasites was also negative. On the day of admission the temperature dropped to 99.4°F and remained normal until June 30, when the patient suffered another chill. On the following morning the temperature was 100.2°F, returning to normal during the same day. He remained afebrile and asymptomatic and was discharged on July 8, no diagnosis having been reached.

On September 9 the patient was readmitted with headaches, chills and fever of 1 week's duration. The chills were true rigors, preceded by nausea and vomiting and followed by long welts on the back and buttocks. A carefully taken history revealed that, in addition to the episode in June, two similar attacks had occurred in early January and mid-March. On both occasions the patient had been treated by a physician with pills for 4 or 5 days, after which the fever subsided.

The past history revealed that in 1945 a diagnosis of latent syphilis, which had been treated with the Army 26-week course of Mapharsen and bismuth† and also 4,000,000 units of penicillin, had been made. He had served in southern France, but not in any tropical theater, and to the best of his knowledge had contracted neither malaria nor any other tropical disease. The review of systems was negative, and he had never noted inguinal adenitis. The family history disclosed that his mother had died of heart disease at the age of 59, a sister had died of unknown cause at the age of 35, and a brother of tuberculosis at 30.

Physical examination disclosed a healthy-appearing, afebrile, young Negro, who was perspiring more than normal. The pupils were equal and reacted to light and accommodation, the extraocular muscles were normal, and there were no abnormalities of the ears, nose or throat. No cervical adenopathy or thyroid enlargement was noted, and the neck was supple. The cardiorespiratory system was normal except for wheezes throughout the whole left lung field, these were absent on later examination. No murmurs, cardiac enlargement or arrhythmia was found. There was slight protuberance of the abdomen, but the liver and spleen were not

†This treatment is as follows: 0.06 gm of Mapharsen intravenously, twice a week for ten weeks, followed by a rest for six weeks, and then another 0.06 gm twice weekly for ten weeks. Bismuth subarsenate, 200 mg intramuscularly is given weekly for five weeks, followed by rest for five weeks, and then six weeks of bismuth, rest for five weeks and, finally five weeks of bismuth.

enlarged and the kidneys were not palpable. According to one observer there was slight bilateral inguinal lymphadenopathy, but this was not confirmed by a second examiner. Genital, rectal and neuromuscular examinations were negative. The diagnosis was "fever of unknown origin."

A ray examination of the chest and analyses of the urine were negative. Examination of the blood revealed a hemoglobin of 12.5 gm. and a white-cell count of 7200. Agglutination tests for *Eberthella typhosa* "O" and H, and *Salmonella schottmulleri* were positive in a titer of 1:80 but negative for *S. paratyphi*, *Pasteurella tularensis*, *Brucella abortus* and *Proteus vulgaris* (Ox19). Two smears for malaria and three blood cultures were negative. The total protein was 6.16 gm per 100 cc., with 4.35 gm of albumin and 1.81 gm of globulin (albumin-globulin ratio of 2.4). Repeated white-cell counts on September 23 and 25 were 5400 and 7600 respectively. Repeated urine analyses were negative. The quantitative Kahn test was reported as 4 Kahn units and the Wassermann test as ++.

For the first 4 hospital days the patient appeared well and was helping the ward attendants. On the 5th day the tem-

other samples of blood. On January 15 and February 3, 1947, the complement fixation titers were 1:40.

### DIAGNOSIS

Four episodes of illness occurred in nine months characterized by chills, fever, diaphoresis and an eruption described by the patient as consisting of welts, each episode being ushered in by headache, anorexia and vomiting. These symptoms and the fever curve were characteristic of a "septic" type of infection. Against a bacterial etiology were the normal white-cell count, several negative blood cultures and negative agglutination tests. (The titers for typhoid and paratyphoid B were those associated with vaccination with "triple typhoid

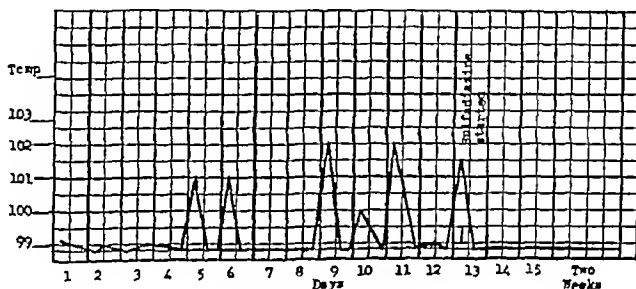


FIGURE 1 Fever Chart

perature at 8 a.m. was 101 F. and the fever curve assumed an intermittent pattern. There were no rigors, but the patient complained of mild headaches.

In the absence of any diagnosis the patient was seen by officers in the Venereal Disease Section whose opinion was that this syndrome was not due to syphilis, since there were no clinical findings of note and he had been given two adequate courses of therapy. The suggestion was made that a systemic infection with the virus of lymphogranuloma venereum could give such a syndrome. Accordingly, a Frei test was done on September 19, and this was markedly positive in 24 and 48 hours. Blood was drawn for complement fixation tests, and +++++ fixation was obtained in a dilution of 1:160. Unfortunately, no further dilutions were done at that time and the serum was lost, so that the true titer was not obtained. Sulfadiazine in full doses was started the presumptive diagnosis being lymphogranuloma venereum.

From the 1st day of antidiazine therapy the temperature dropped and never rose during the 2 weeks in which the drug was administered (Fig. 1). The patient was sent on convalescent furlough on October 4 and returned on October 16, when he was well and had no complaints. Further complement fixation tests were done to completion at that time and +++++ reactions were obtained in dilutions up to and including 1:640.

The patient was seen again on November 12. By that time he had gained 15 pounds and expressed the opinion that he had not felt so well the whole year. He had experienced no recurrence of any symptoms and the +++++ titer was 1:320.

Shortly after this last examination the patient was discharged from the Army. He co-operated by sending two

vaccine.") During this diagnostic impasse the possibility of a systemic infection with a specific Frei arose, and the diagnosis was made on the basis of a positive Frei test and a positive complement-fixation test. He was then treated with sulfadiazine, and the response was gratifying. Although the therapeutic response is not a specific reaction, the complement-fixation and Frei tests are.

In any group of adult Negroes, a considerable number will be found to have positive Frei tests, various studies disclosing anywhere from 10 to 40 per cent, or more.<sup>1</sup> Thus, the establishment of a diagnosis on the basis of this test alone is hazardous.

The complement-fixation test done in this laboratory uses "Lygranum CF"<sup>2</sup> from a purified preparation of virus grown on chick-embryo yolk sac.<sup>3</sup> The antigen is a specific antigen and has few side reactions of note.<sup>3</sup> In a survey conducted at this hospital no positive reaction (+++++) has been encountered in a serum dilution higher than 1:20 in persons without either clinical lymphogranuloma

<sup>2</sup>The antigen used in this and related studies was supplied by E. R. Squibb & Sons, through the courtesy of Dr. Charles H. Mason.

or a recent history of the disease. Thus, the initial titer of 1 640 is a highly significant one and cannot be considered a false positive. The high titer is also consistent with the long duration of the illness, and a fall in titer is significant diagnostically, as well as therapeutically, since it occurs frequently after treatment with sulfadiazine. A later sample of convalescent serum was sent to the Virus Laboratory of the Army Medical School, where Dr. Joseph Smadel did complement-fixation tests using a different antigen.\* He reported the results as positive in a lower titer (1 32) but was able to ascribe the difference to the use of different antigens.

A diagnosis based on this test raises the problem of infection with a related virus, such as that of psittacosis, the pneumonitis virus of Eaton, the meningopneumonitis virus of Francis and Magill, trachoma and inclusion blenorrhea virus and the virus of mouse pneumonitis (Nigg). The viruses of Nigg and Francis do not produce known infections in human beings, and in the absence of any eye disease, it is hardly possible to incriminate the viruses causing trachoma or inclusion blenorrhea. The absence of any symptoms or signs referable to the respiratory system and the negative x-ray examination of the chest tend to rule out the psittacosis and pneumonitis (Eaton) viruses. In addition, neither of these infections responds to sulfadiazine in such dramatic fashion, nor do they pursue the relapsing course observed in the case reported above. The combination of clinical course, positive Frei test and a high titer of specific complement-fixing antibodies served to establish the diagnosis in this case.

In the past, the diagnosis of these cases was almost impossible early in the disease and could be made only when, after prolonged pyrexia, sometimes extending for over a month, an inguinal mass appeared and suppurated in characteristic fashion. Kornblith<sup>3</sup> reported 2 cases in which this was the sequence of events. In both, there was a septic type of fever of three weeks' duration, the diagnosis was made in one after bilateral suppurative adenitis had supervened and in the other by biopsy of an inflamed inguinal lymph node. D. Luger<sup>4</sup> describes a case of prolonged fever without any localizing symptoms, which was diagnosed as lymphogranuloma venereum by biopsy of a slightly enlarged non-tender inguinal lymph node. In each of these cases there was a history of copulation with Negroes. It is also noteworthy that in each case in white men the diagnosis was made on an average of one month after the onset of fever. Other cases have been reported by Giacardy<sup>5</sup> and Chevallier and Bernard,<sup>6</sup> and Stannus<sup>7</sup> speaks of a typhoidal state occurring in this illness.

An interesting series of infections was reported by Harrop, Rake and Shaffer,<sup>8</sup> involving 3 laboratory workers. One handled infected mice, and 2 inocu-

lated mice intranasally with lymphogranuloma virus. In each of these cases there was headache accompanying chills, sweats and a spiking temperature curve, 2 patients had cervical adenopathy. One of these was given an average of 5 gm. of sulfadiazine daily for nine days, the temperature became normal in seventy-two hours, and there were subsequently no residua of the infection. Another patient had a similar clinical picture and was treated for three days with sulfathiazole (27 gm.). This episode was curtailed, but three recrudescences occurred. During the last attack the treatment with the sulfonamide was vigorous (100 gm.), and no recurrences were noted. There was a rise in complement-fixing antibodies in each case, and positive Frei reactions were present. This latter test became negative in the 2 patients who were given adequate sulfonamide therapy while complement-fixing antibodies were still present in declining titers.

#### PATHOGENESIS AND CLINICAL COURSE

Lymphogranuloma infection can occur in varying severity. Some infections are so mild as to be sub-clinical and are detectable only by the Frei test and by quantitative complement-fixation or virus-neutralization studies.<sup>1</sup> The most frequent forms clinically are those causing inguinal adenitis and proctitis. In these forms the "systemic" signs vary widely in severity, so that some patients are free of fever, malaise and headache, and others are so profoundly prostrated that bacterial sepsis is imitated. Similarly, the lymph nodes may not appear abnormal on physical examination, or they may form an abscess the size of an orange. Thus, any combination of systemic signs and the various grades of lymphadenitis may be present, even the complete absence of both or either.

Histologically, the lymph nodes in this infection show multiple abscesses of varying sizes, which characteristically have a radiate arrangement of the lining epithelioid cells. As the process extends, large accumulations of pus may occur, and when this material is collected and inactivated with heat, it may be used as Frei antigen. When the material or heated cultivated virus is injected intravenously into normal people no reaction is noted, but in infected persons, a temperature rise is noted in twelve to eighteen hours. This reaction was used diagnostically and therapeutically in the past.<sup>9</sup> The fact that material, which is present in the body, is capable of exciting a febrile response suggests a likely method of pathogenesis of the generalized symptoms.

Rake and Jones<sup>10</sup> isolated a fraction from infected yolk and yolk sac that was lethal for mice and postulated that this substance was responsible for the systemic symptoms of this disease. The substance was found in the same fraction that contained the viral elementary bodies, from which it was not separated. It is possible that the "toxic factor" is

\*A suspension of washed psittacosis elementary bodies.

inherent in the virus particles in the manner of an endotoxin

Although the virus has never been isolated from the blood, there is considerable evidence that it can be spread throughout the body by the circulation. Its occurrence in the spinal fluid in patients with inguinal adenitis, but without meningitis, has been described,<sup>11</sup> and meningitis and meningoencephalitis due to this virus has been mentioned in several reports.<sup>12-14</sup> It has been noted experimentally that meningoencephalitis can be produced in mice after intraperitoneal inoculation of virus if the brain is simultaneously traumatized aseptically.<sup>15</sup> It is difficult to conceive of a method of spread in such cases except by the blood stream.

It appears, then, that in the type of infection described above, the virus remains hidden in the body, probably in the lymph nodes, where it may produce anatomic, but subclinical, changes. Periodic release of virus into the blood stream results in symptoms of a general systemic infection similar to those found in bacterial sepsis.

### TREATMENT

Lymphogranuloma may recur unless treatment with sulfadiazine is vigorous and prolonged. Full therapeutic doses cause abrupt remission of systemic symptoms. In Harrop's<sup>6</sup> report, three relapses occurred in a patient who had received sulfonamide for short periods. During the fourth attack, treatment was given for over twenty days, and no recurrences were noted. At this hospital full doses of sulfadiazine (1 gm. every four hours, day and night) have been used for two weeks unless symptoms persist longer. This was the treatment given in the case reported above, and the patient has had no recurrence to date. It is my belief that shorter and less intense courses will be less efficacious.

### Discussion

This type of infection is not fatal. However, extension to the brain and meninges or to the bones and joints is possible,<sup>16</sup> and in view of the prompt response to sulfadiazine, it is desirable that the diagnosis be made early. The majority of cases betray themselves after a period of months, but

the patients become debilitated, anemic and chronically ill. The essential features of the infection are chills, a temperature with daily spikes of fever, sweats, headaches, a normal or slightly elevated white-cell count and a history of sexual promiscuity. Thus, in all cases of fever of hidden origin, when laboratory aid is sought, this type of infection should be considered. The quantitative complement-fixation test will substantiate or eliminate the diagnosis. The procedure is a simple one and can be done by any laboratory equipped to do Wassermann tests.

### SUMMARY

An unusual syndrome caused by the virus of lymphogranuloma venereum is described.

The diagnosis was made by the use of quantitative complement-fixation tests for the virus.

The pathogenesis of this type of infection is discussed.

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## THE DISABLED VETERANS OF WORLD WAR II\*

### Analysis of 600 Cases Examined at Harvard University

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SINCE the termination of hostilities, many sick and wounded veterans have been returning to universities to complete the requirements of their college and graduate-school academic assignments, under the G I Bill (Public Law 346) and the Rehabilitation Bill (Public Law 16) of the Seventy-Eighth Congress. The disabled veteran has been epitomized in the press, radio and motion pictures, and although much is sponsored for his good and although many benefits have been provided for him by a generous government, it seems appropriate to call attention to what a group of six hundred dis-

abled veterans, whether service-connected or not, and that each of these veterans is entitled to the free filling of medicinal prescriptions at the pharmacist's, as well as to free eyeglasses and to free medical consultation service. Through the professional staff of the Hygiene Department and through its board of consultants in the specialties of medicine, a complete medical service is provided free for the disabled veteran at Harvard University. The professional fees of the consultant board are computed at the Blue Shield fee-schedule rate and billed to the Hygiene Department, the University being reim-

TABLE 1 *Disabilities among 600 Veterans Examined at Harvard University*

COMBAT-INCURRED DISABILITIES	NO OF CASES	PER-CENTAGE	NONCOMBAT-INCURRED DISABILITIES	NO OF CASES	PER-CENTAGE
Bone and joint wounds	84	30.0	Medical disease	146	37.9
Superficial wounds	72	25.7	Orthopedic conditions	87	22.6
Neurosurgical wounds	27	9.7	Neuropsychiatric conditions	52	13.5
Amputations	27	9.7	Trench foot	34	8.8
Frost bite	18	6.4	Neurologic conditions	13	3.4
Thoracic wounds	14	5.0	Vascular conditions	10	2.6
Abdominal wounds	11	3.9	Ear, nose and throat conditions	8	2.1
Plastic-repair wounds	5	2.8	Ophthalmologic conditions	7	1.8
Ophthalmologic wounds	5	1.8	Deafness	5	1.3
Ear, nose and throat wounds	5	1.8	Plastic surgery	5	1.3
Urologic wounds	4	1.4	Dermatologic conditions	6	1.5
Oral and dental wounds	3	1.1	Cancer	5	1.3
Vascular surgical wounds	2	0.7	Abdominal conditions	3	0.8
Total	280		Dental conditions	2	0.5
			Urologic conditions	1	0.3
			Thoracic surgery	1	0.3
			Total	385	
			Multiple surgical diagnoses	27	
			Multiple medical diagnoses	16	
			Surgical and medical diagnoses	22	
			Total	65	
			Total diagnoses	665	
			Total cases seen	600	

abled veterans in one of our universities represent in the way of disabilities.

Harvard University has negotiated a contract with the Veterans Administration, whereby all students enrolled under Public Law 16 are cared for by the Hygiene Department. The responsibility for the entire health and sickness program provided in this law applicable to Harvard students is delegated to the university health department. It is true that very few doctors appreciate the fact that the students receiving benefits under this law are entitled to free care for medical and surgical con-

ditions, whether service-connected or not, and that each of these veterans is entitled to the free filling of medicinal prescriptions at the pharmacist's, as well as to free eyeglasses and to free medical consultation service. Through the professional staff of the Hygiene Department and through its board of consultants in the specialties of medicine, a complete medical service is provided free for the disabled veteran at Harvard University. The professional fees of the consultant board are computed at the Blue Shield fee-schedule rate and billed to the Hygiene Department, the University being reim-

#### NONCOMBAT-INCURRED DISABILITIES

In an analysis of six hundred consecutive examinations of disabled veterans, it is apparent that a large group of noncombat-incurred disabilities were received in line of duty. With corrections for multiple diagnoses, the noncombat-incurred disabilities represent 60 per cent of the entire group. Perhaps of even greater significance is the fact that 38 per cent

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1947.

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of these disabilities were due to medical disease (Table 1). Furthermore, an additional 23 per cent — an even greater number of men than that of those who had combat-incurred bone and joint wounds — were caused by orthopedic conditions. Perhaps as the result of screening by the Board of Admissions, neuropsychiatric disabilities do not loom large in this group.

If one considers the noncombat-incurred disabilities from a practical point of view, it is obvious that many of these men have reached the optimum

TABLE 2. *Noncombat Incurred Disabilities for Which Compensation Has Been Granted*

MEDICAL DISEASE	No. of Cases
Malaria	35
Cardiovascular disease	34
Gastrointestinal disease	24
Allergy	12
Tubercle disease	10
Rheumatoid arthritis	8
Central-nervous-system disease	1
Diabetes mellitus	1
Acrocyanoosis	1
Total	147*

\*In 1 case more than one diagnosis was made; hence the actual total of patients is 146.

recovery point. Table 2 presents the pathologic entities for which disability compensation has been granted. It is not practical to list all the orthopedic conditions involved in the grant of compensation (Table 3), but *per planus*, internal derangements of the knee and back strains represent 50 per cent. Most of the patients are not incapacitated from accomplishing their academic assignments and re-

TABLE 3. *Noncombat Incurred Orthopedic Conditions Involving Compensation*

LOCATION	No. of Cases
Upper extremity	18
Back	25
Lower extremity	45
Total	88*

\*In 1 case more than one diagnosis was made; hence the actual total of patients is 87.

quire no further medical treatment, even though they still receive disability compensation. In other words, the Government appears to be maintaining certain disability allowances beyond the point of necessity. For example, one man has a 100 per cent disability rating for chronic infections mononucleosis, the most recent symptoms of which occurred sixteen months prior to the most recent physical examination. In the category of noncombat-incurred disabilities, 114 men with medical diseases are receiving \$4570 per month in compensation, an average of \$39.74 per man, and 50 men with

orthopedic conditions are receiving \$1394 per month, an average of \$27.88 per man — a total of

TABLE 4. *Bone and Joint Wounds Sustained in Combat*

LOCATION OF WOUND	No. of Cases
Upper extremity	
Fracture compound comminuted	39
Joint wound without bone involvement	9
Humerus wound without fracture	1
Total	49
Chest	
Fracture compound comminuted, sternum ribs or vertebra	4
Total	4
Lower extremity	
Fracture compound comminuted	41
Joint wound without bone involvement	3
Muscle-tissue wounds	4
Total	48
Total	101*

\*There were 17 cases with more than one diagnosis; hence the actual total of patients is 84.

\$5964 for these two groups, or an average of \$36.15 per man.

#### COMBAT-INCURRED DISABILITIES

The largest group of diagnoses of combat-incurred disabilities fall in the classification of bone-and-

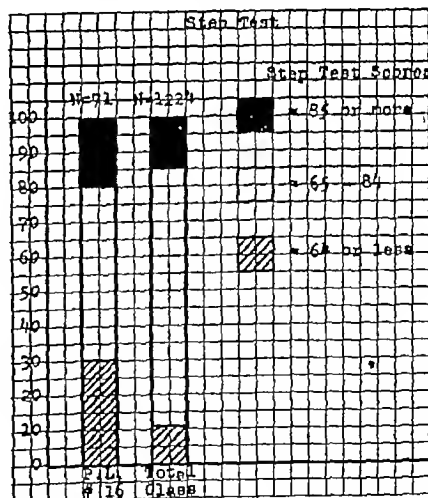


FIGURE 1. *Physical Fitness in Freshman Class, Harvard College (September, 1946)*

joint wounds (Table 4). Forty-six of these men are receiving disability compensation totaling \$2952 per month — an average of \$64.17 per man. Most of them had a compound fracture, with or without serious complicating involvement.



nerves or other tissues. Since there are still over 5000 men with battle wounds in Army hospitals today, it is obvious that this group does not represent the most serious types of cases. Active osteomyelitis was a rare finding, only 2 cases being observed among the 84 men with healed compound fractures. Only 1 of these patients required hospitalization owing to a minor recurrent abscess due to a small sequestrum. The men with bone-and-joint injuries and those with peripheral-nerve wounds comprise the majority of patients requiring

of those excused for medical reasons among the disabled veterans exceeded by only 3 per cent the figure for the class as a whole, and likewise, the percentages of those qualifying after instruction were reasonably alike in both groups (Fig 2). In an analysis of the participation of 156 disabled veterans and 1786 normal veterans the incidence of the former who were excused from the compulsory sports program was only 5.4 per cent greater than that of the latter (Fig 3). Even more significant is the difference of 1.7 per cent in contact-sports participation between the disabled and nondisabled veteran. From these data, it can only be concluded that many veterans classified as disabled have insignificant disabilities. With over 2,500,000 veterans of World War I and World War II classified as disabled, it appears that many of these men have relatively minor or insignificant handicaps.

### REHABILITATION

Since corrective exercises are of greater importance than physical therapy in the rehabilitation of men with late convalescent disabilities, the Hygiene Department has developed such a program. Mr. Lloyd C. Harper, who has had considerable ex-

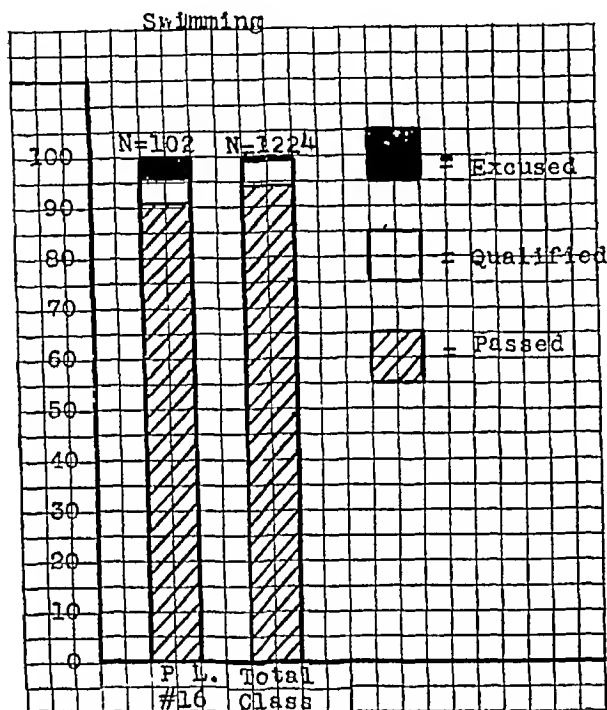


FIGURE 2 Physical Fitness in Freshman Class, Harvard College (September, 1946)

further medical treatment, physical therapy and remedial exercise.

### APPRAISAL OF DISABILITY

Perhaps an adequate method of appraising the degree of disability of these veterans is to compare the results of the compulsory physical-training program required in the freshman class. All freshmen are required to take a physical-fitness test known as the "Harvard Step Test," in which they are scored according to an accepted standard of normals. A score of 85 or above is rated as excellent, one of 65 to 84, as satisfactory, and one below 65, as unsatisfactory. The 71 disabled veterans had a higher percentage of excellent ratings than the freshman class as a whole (Fig 1)—an unanticipated finding. As might have been expected, however, a smaller percentage of disabled veterans completed the test satisfactorily, and a greater percentage failed. In the required swimming test, the incidence

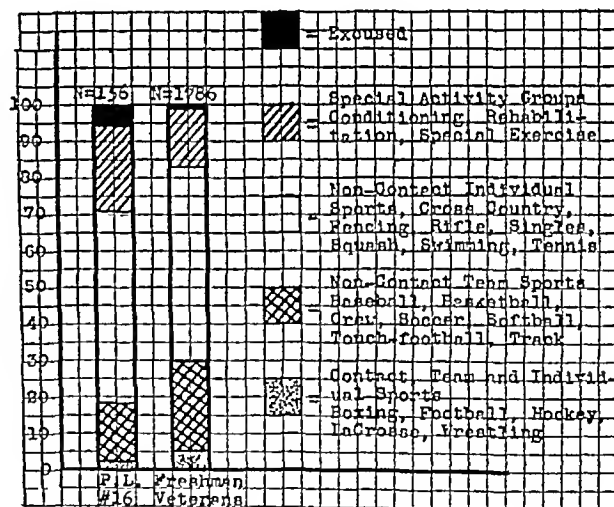


FIGURE 3 Comparison of Sports Participation between Public-Law-16 Students and Freshman-Class Veterans (Summer, Fall and Spring Terms, 1946-1947)

perience with the Army reconditioning program, is responsible for these exercises under medical guidance. The Department of Physical Training has provided the gymnasium and has obtained the necessary apparatus and equipment. Individual treatment is afforded all cases at first. With progress in restoration of function, group exercises, including group sports, are recommended. Rowing, swimming, basketball, volleyball and softball are group activities usually provided. There are 10.5 per cent of the 600 disabled veterans now participating in this program.

Those who are familiar with the program of reconditioning and rehabilitation in the Army and Navy hospitals appreciate the values of adequate convalescent care. In returning to civilian life, the severely disabled veteran turns to his family physician, expecting that his permanent disabilities will be treated and improved. Deaver<sup>1</sup> described methods for the rehabilitation to economic independence of the physically handicapped civilian at the Institute for Crippled and Disabled in New York City. Lippman<sup>2</sup> has reported a program of convalescent reconditioning for civilian hospitals. Most hospitals, however, are unable to find space or to obtain the necessary specialized personnel for such an undertaking. Aitken<sup>3</sup> has described an outstanding medically supervised program of rehabilitation, limited in its clientele, for the civilians of New England. Large communities need facilities for rapidly restoring convalescent disabled civilians to gainful occupations. The patient in late convalescence from a serious disability today is the forgotten patient in civilian practice. The rewards of adequate recovery are immeasurable. To increase the average annual wage of 44,000 handicapped retrainees under the 1944 training program of the Office of Vocational Rehabilitation from \$148 to \$1768 is a noteworthy accomplishment.<sup>4</sup> A similar

program would restore a large part of our society — reported to number over 20,000,000\* — from dependency on state, county or city charity to economic independence and productivity.

#### SUMMARY

A study of 600 disabled veteran students in Harvard University demonstrated that 60 per cent of the disabilities are noncombat-incurred and do not cause interference with the pursuit of academic assignments, that a comparison between the abilities of the disabled veteran freshman and those of the class as a whole to participate in compulsory-exercise programs demonstrates an insignificant percentage variation between the two groups, and that the 10.5 per cent of this group requiring further rehabilitation is taking part in a medically supervised remedial-exercise program.

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## TOXIC EFFECTS OF GASES AND VAPORS\*

### Mechanism of Poisoning by Volatile Solvents

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ACCIDENTAL poisoning as a result of the inhalation of toxic gases or vapors is encountered with discouraging frequency. The number of reports in the current literature suggests that the incidence of such poisoning is on the increase. The basic reason for this rise is the recent, rapid increase in the development and industrial use of volatile organic solvents. Unfortunately, accurate statistics concerning these cases are not available in this country for a variety of reasons. The reporting of occupational disease is encouraged by the Commonwealth of Massachusetts, but is not mandatory, complete statistics are therefore not available from this source. Compensation-board records are not too helpful, since their opinions and findings are frequently not accompanied by sufficient objective evidence to permit an evaluation of the cases in question. Furthermore, there is no way to deter-

mine the incidence of accidental poisonings occurring in the home, which may not be recognized or if recognized but not fatal, are usually not reported. The situation regarding determination of the incidence of such poisoning is roughly similar in other states, some being slightly better and many far worse than Massachusetts.

It is believed that many illnesses resulting from the inhalation of toxic gases or vapors are ascribed to other causes. Failure to recognize the etiologic role played by a toxic agent in a given illness stems from a variety of factors. The syndrome produced may resemble in every particular one of several common organic diseases with which the physician is more familiar. The patient is frequently not aware that the air he is breathing contains a noxious agent, and fails to associate the breathing of some odd-smelling but essentially nonirritating air with the occurrence of illness ten days or two weeks later. Many physicians do not appreciate the importance of the respiratory tract as an avenue for the absorption and elimination of large doses of

\*Part of a symposium on industrial medicine presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1947.

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many toxic agents, and either do not elicit a history of exposure or do not recognize the significance of such a history. It is perhaps advisable, therefore, to present briefly some of the basic principles involved in the absorption of toxic gases and vapors, before consideration of the type of poisonings that

TABLE 1 *Effect of Solubility on Blood Concentration and Total Body Content \**

SUBSTANCE	COEFFICIENT OF DISTRIBUTION	BLOOD CONCENTRATION AT EQUILIBRIUM mg /liter	TOTAL WEIGHT IN BODY gm
Carbon disulfide	2.5	0.25	0.0175
Ethyl ether	15.0	1.5	0.1050
Ethyl alcohol	1300.0	130.0	9.1000
Methyl alcohol	1700.0	170.0	13.9000

\*Air concentration, 0.1 mg per liter

commonly occur and are believed to be unrecognized in many cases

#### ABSORPTION AND ELIMINATION OF GASES AND VAPORS

As air containing a noxious agent is inhaled, some of this air reaches the alveoli. The air in the alveoli comes into virtually complete equilibrium with the

returning to the lungs gradually contains more of the gas or vapor, in solution, so that smaller amounts can be absorbed into the blood from the alveoli and a state of equilibrium — saturation — is gradually approached. When this occurs the body contains as much of the gas or vapor as it can hold in equilibrium with the concentration existing in the inspired air. Under these conditions, the expired air will contain as much of the substance as the inspired air, and additional absorption will occur only as the material already in the body is metabolized or eliminated via other channels.

The actual amount of a given substance that the body can contain when in equilibrium with a given air concentration is quite variable, depending essentially on the solubility of the substance in blood and tissue. It may be expressed in terms of the coefficient of distribution, which may be defined as the ratio of the weight of gas or vapor in equal volumes of air and fluid that are in gaseous equilibrium. A substance that is relatively insoluble in blood or tissue has a low coefficient of distribution, whereas one highly soluble in blood or tissue has a high coefficient (Table 1). The solubility of the substance in blood or tissue also influences the total amount of the substance entering the body;

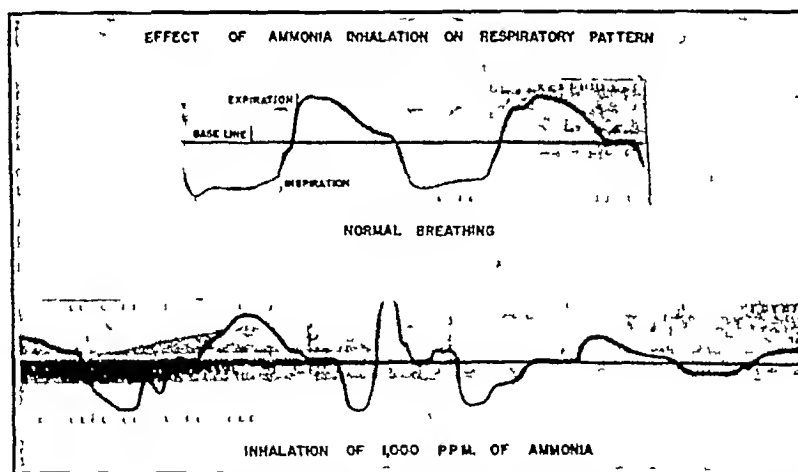


FIGURE 1 *Representative Respiratory Pattern of a Subject Exposed to 1000 Parts of Ammonia per 1,000,000 Parts of Air*

*The upper record shows the normal response, and the lower that after exposure to ammonia*

blood almost instantly. This, of course, results in a marked lowering of the concentration of the substance in the alveolar air as the blood concentration rises, and less of the toxic agent is exhaled than was taken in. The blood leaving the lungs contains an appreciable amount of the toxic material, which it in turn gives up to the tissues, until blood and tissues reach equilibrium with one another. As the above process is repeated, the capacity of the blood and the tissues to take up more of the agent at the pressure maintained in the alveoli is gradually exhausted, and consequently the venous blood

an average-sized man in equilibrium with air containing 0.1 mg per liter of carbon disulfide will contain a total dose of slightly less than 20 mg of carbon disulfide, whereas a man in equilibrium with the same air concentration of methyl alcohol will contain nearly 14 gm of this substance, or about seven hundred times as much.

Equilibrium is approached rapidly with the relatively insoluble substance, only a small amount of which is required to saturate the body, but is approached slowly with the highly soluble substance, since a large amount is required. Elimina-

tion of substances from the body via the lungs occurs as the reverse of absorption, once exposure is discontinued. The situation is analogous to the filling and emptying of tanks of various sizes through a pipe, the size of the tank representing the solubility of the material in the body and the diameter of the filler pipe the rate of exchange between alveolar air and blood. If the substances have a low coefficient of distribution, the tank is small, equilibrium is achieved rapidly, and elimination via the lungs takes only a short time. If the substances have a high coefficient of distribution the tank is large, equilibrium requires many hours of exposure, and elimination is correspondingly protracted. Some of these absorbed substances, how-

mode and type of interference with the breathing pattern, a series of experiments was carried out in which human subjects inhaled ammonia or trichlorethylene vapor from a large glass-lined tank through a rubber facepiece. The concentrations in the tank were achieved by complete evaporation of an amount of trichlorethylene or concentrated ammonium hydroxide that produced the desired concentration in the volume of air contained by the tank. The tank was connected to the subject's breathing mask by a system of valves that permitted rapid switching from room air to tank air without interruption of the breathing cycle.

The respiratory pattern was recorded by means of the pneumotachograph developed by Silverman,<sup>1</sup>

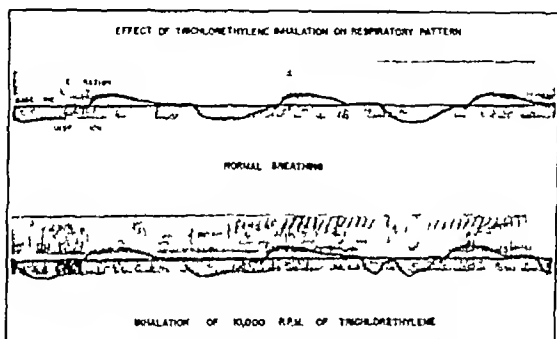


FIGURE 2 Representative Respiratory Pattern of a Subject Exposed to 10,000 Parts of Trichlorethylene per 1,000,000 Parts of Air. The upper record shows the normal response and the lower that after exposure to trichlorethylene vapor.

ever, are either eliminated by other channels or metabolized in the body. This is analogous to the situation existing when one fills a tank with an open drain—it takes a long time to fill it, but emptying proceeds rapidly.

Exposure to many toxic gases and vapors is self-limiting because of the unpleasant and irritating effects produced by their inhalation. Serious poisoning due to the prolonged inhalation of such agents occurs infrequently, because the exposed person usually removes himself voluntarily from the unpleasant atmosphere. Many other agents are not unpleasant to breathe in concentrations that are capable of producing serious injury to health, so that a person may undergo a sufficiently prolonged exposure to permit the absorption of amounts of the gas or vapor that will produce injury to the body. One of the factors that appears to determine whether a given exposure will be tolerated or will be voluntarily discontinued is the production of sufficient irritation of the respiratory tract to upset the normal breathing pattern. To determine the

which indicates the rate and volume of inspiration and expiration by recording the instantaneous pressure differential created by air flow through a fine mesh screen inserted in a breathing mask. The resistance to respiration of this device is negligible. A representative respiratory pattern of a subject exposed to 1000 parts of ammonia per 1,000,000 parts of air is presented in Figure 1. The upper record is the normal pattern, whereas the lower is the response following exposure to ammonia. It is evident that the breathing pattern is considerably altered. In general, exposure to an irritating gas such as ammonia resulted in coughing, reduction in the depth of inspiration and restraint of breathing. The subjects wished to avoid any further exposure. The breathing pattern after exposure to 10,000 parts of trichlorethylene per 1,000,000 parts of air (1 per cent by volume) is presented in Figure 2. Again, the upper record represents the normal curve for the subject, and the lower shows the response following exposure to trichlorethylene vapor. There is no essential difference between the two patterns

in fact, they could almost be superimposed except for the occurrence of a swallow during the third inspiration. This lack of any significant alteration in respiratory pattern was accompanied by a subjective willingness to continue the exposure, despite the rather strong sweet odor noted at this high concentration.

This failure to alter the breathing pattern and willingness to continue exposure to a concentration of a chlorinated hydrocarbon that approaches the anesthetic level is considered most significant, since far lower concentrations (500 parts per 1,000,000) are capable of producing organic damage following prolonged or repeated exposure.<sup>2</sup> It is not surprising, in the light of these observations, that dangerous exposures with the absorption of sufficient material to cause serious damage to the body may proceed without any awareness or recollection on the part of the patient. Such exposures will be avoided only if the patient is aware of their possible consequences, or if others who are aware of them make such exposure impossible.

At present the medical profession and industrial hygienists are well aware of the hazard associated with many solvents, and serious poisoning from these sources is occurring less and less frequently. For example, carbon disulfide and benzene no longer menace the health of workers as they did ten or twenty years ago, since the hazards are recognized and controlled.

New solvents and volatile chemicals, however, some of which may be capable of causing serious illness, are constantly being introduced in industry and to a lesser extent turned loose on an unsuspecting public. These illnesses will be attributed to the agents producing them only if the profession is alert to the possibility that a given illness has developed as a result of exposure to a toxic agent. Therefore, one should be aware of the general type of symptomatology and findings that may follow exposure to toxic gases or vapors, especially conditions developing after exposure to agents that are not unpleasant or irritating to breathe. The victim may fail to remember having been exposed and probably will not spontaneously disclose a history of exposure since, in his opinion, the disease he is suffering from is unrelated.

Disease of the liver or impairment of blood-cell formation has long been associated with solvent vapor exposures. The possibility of a toxic exposure is therefore usually thought of and investigated in patients with unexplained jaundice or with anemia or leukopenia. Many toxic vapor exposures may fail to give either of these reactions, however, resulting instead in the development of a nephritis that clinically is readily mistaken for ordinary glomerular nephritis. Since many physicians are not aware of the frequency of toxic nephritis due to single or multiple exposures, they may fail to inquire about previous exposure in a patient with

evidence of renal disease, when they would go to considerable lengths to determine such exposure in a patient with anemia or evidence of seriously impaired liver function. The failure to associate nephritis with toxic injury is rather surprising, since many cases of acute toxic nephritis have been reported following the inhalation of carbon tetrachloride.<sup>3-5</sup> Other agents are also capable of producing kidney damage. For example, an acute toxic nephritis recently occurred in a fifty-three-year-old shipping clerk who had undergone relatively brief but severe exposure to a solvent mixture containing 80 per cent toluene. This case was almost dismissed as one of acute glomerular nephritis, since the patient did not at first remember his exposure. The possibility of a toxic nephritis was considered when it was determined that he might have been exposed to carbon tetrachloride. When it was discovered that the solvent vapor to which he was exposed was 80 per cent toluene and 20 per cent ethyl acetate, the possible toxic nature of the kidney disease was almost dismissed, for toluene and ethyl acetate are not generally associated with the occurrence of nephritis. The facts that toluene exposure is capable of producing renal lesions in animals<sup>6</sup> and that the exposure was related to the onset of the nephritis and to the subsequent course of this illness were finally accepted as sufficient evidence to justify a diagnosis of toxic nephritis due to toluene. This case is cited to emphasize the fact that nephritis may occur as a result of serious exposure to toxic gases and vapors, even though the agent in question has not previously been recognized as being capable of inducing such a syndrome in man.

Such cases will be correctly diagnosed only if the medical profession considers the possibility of a toxic agent in cases that appear to be glomerular nephritis, obscure anemias or atypical liver disease. The possibility of any exposure to a toxic gas or vapor should be investigated in every such case, and if any suggestive history is elicited, the circumstances should be investigated thoroughly and the nature of the gas or vapor determined accurately. Finally, the fact that a given syndrome has not previously been reported as resulting from the agent in question does not rule out the possibility that such cases have occurred and gone unrecognized.

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## MEDICAL PROGRESS

## RADIATION THERAPY

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THE basic principles of radiation therapy have undergone no radical changes during the last five years. The science of physics has contributed fresh means of accomplishing what the radiation therapist has always attempted: maximum selective destruction of the tumor with minimal damage to the normal tissues. These new contributions include apparatus for the generation of extremely high as well as extremely low voltages. The term "super-voltage," which once designated a charge of 400,000 volts, must now be applied to voltages in the range of 1,000,000 to 100,000,000. These powerful rays have the advantage of greater penetration, whereas the units of extremely low voltage have correspondingly low penetrability and are comparable in action to radium.

The development of the atomic bomb has provided a large supply of radioactive isotopes, formerly produced in small quantities by the cyclotron. These elements are now being used extensively as therapeutic agents, only time will evaluate their efficiency in the treatment of disease. The recent development of the betatron has initiated the experimental phases of therapy by means of high-energy electrons.

Large amounts of radiation are necessary for cancerocidal effect on tumors, notwithstanding damage to the skin and surrounding tissues. The injurious changes to structures in the path of the radiation become relatively unimportant as compared with the prime objective of tumor destruction. It is with this in mind that newer methods of radiation therapy are being evolved to accomplish maximum tumor destruction without ultimately damaging normal structures.<sup>1</sup> To approach this ideal, a proper perspective of tissue tumor sensitivity and the consideration of portals of treatment and physical factors are essential.

The previous methods of expressing the dosage in air or on the skin surface were both confusing and unsatisfactory. More recently the measurements of so-called "tumor dose" have given a more accurate description of the amount of radiation delivered to the center of the tumor. Quimby<sup>2</sup> and others<sup>3-5</sup> have provided many of the physical data for the compilation of these measurements. In

addition, radium dosages are now expressed in gamma roentgens ( $\gamma r$ ), giving a measurement comparable to that based on the roentgen (r), which is used in x-ray therapy. The earlier method of expressing doses in milligram or millicurie hours did not take into consideration the bulk of the tumor.

Tumor doses vary with different tissues. Warren<sup>6</sup> has noted variations in the response of tumors to irradiation. These tumors have been divided into the following groups: radiosensitive, radioresponsive and radioresistant. Warren<sup>7</sup> states "Radiosensitive tumors are not necessarily radiocurable. Often they are not, recurring in a resistant form after the initial regression." Certain radioresistant tumors, on the other hand, can be cured by adequate irradiation.

## BREAST

*Carcinoma*

Martin<sup>8</sup> states that only 25 per cent of all patients with carcinoma of the breast can hope for surgical cure. The remaining 75 per cent must therefore receive some form of radiation therapy.

The indications for radiation treatment of this disease are intimately associated with the criteria for operability. Radiation therapy is theoretically not indicated in cases that are operable. The criteria for operability have been fully described by Haagensen and Stout.<sup>9</sup> Borderline cases may be subjected to surgery, and some investigators<sup>10,11</sup> believe that these patients require postoperative therapy to ensure optimum results. The regions treated under these conditions include the immediate areas of lymph drainage—namely, the axilla, the supraclavicular and infraclavicular regions and the mediastinum.

X-ray therapy is the method of choice in the treatment of inoperable carcinoma of the breast.<sup>8,12</sup> Lenz<sup>13</sup> emphasizes the value of large cancerocidal doses and employs tumor doses as high as 6000 to 8000 r, which are given through multiple portals to the breast and axilla. When a dose of less than 5500 r was given, the tumor was not grossly eradicated. In his series of 48 patients treated with 6000 r or more, 10 were clinically free of disease five years later. Martin<sup>8</sup> treats inoperable breast neoplasms with interstitial radium-needle implantation to lessen the danger of pulmonary fibrosis, which may occur with roentgen therapy.

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## UTERUS

*Carcinoma of the Fundus*

Carcinoma of the uterus can be treated by surgery, irradiation or a combination of both. Meigs<sup>13</sup> states, "There is no doubt that nearly all workers in this field believe that the combination treatment is most satisfactory." Corscaden<sup>14</sup> believes that the rate of five-year cures can be increased to 80 per cent with the combined method. Heyman and Benner<sup>15</sup> reported the largest series treated by irradiation alone. They gave their relative over-all cure rate as 64.9 per cent. The rate with radiation therapy alone depends on the uniform distribution of the radiation to the tumor. Many methods have been devised to obtain this effect.<sup>16-18</sup> Heyman et al.<sup>19</sup> pack the uterus with radium capsules, and their results show that excellent distribution is thus obtained.

The technic generally advocated is diagnostic curettage, followed by the immediate implantation of radium in cases of cancer.<sup>19-22</sup> The dose is carefully planned for each patient. Four to eight weeks later, surgical extirpation is performed in patients who are considered good surgical risks. If surgery is contraindicated curettage is repeated, and radium is reapplied if necessary.

Miller and Henderson<sup>22</sup> have reported 77 per cent five-year cures and 65 per cent ten-year cures from the combined method of treatment. Scheffey and his associates<sup>21</sup> give a five-year survival rate of 90 per cent for patients receiving adequate surgical treatment and irradiation by a planned technic.

*Benign Uterine Bleeding*

Radiation therapy for benign bleeding at the menopause must always be preceded by diagnostic curettage to rule out cancer. Irradiation does not replace surgical procedures, but it has a definite place in the treatment of menopausal uterine bleeding. Some of the indications for irradiation rather than surgery include poor surgical risks, refusal of major operation and pathologic states elsewhere in the body. Irradiation is contraindicated in myomas larger than the size of a grapefruit and extending out of the pelvis into the abdominal cavity, and in young patients for whom myomectomy is possible.<sup>23</sup> Radium is contraindicated in patients with submucous fibroids because necrosis may occur, causing persistent bleeding, x-ray therapy, however, may be used in these cases. Crossen and Crossen<sup>24</sup> have treated 526 cases of bleeding due to uterine myoma with radium, attaining successful results in 490 cases (93 per cent). Schmitz and Towne<sup>25</sup> have successfully treated 412 cases with either x-ray or radium. Of the many methods proposed for the treatment of benign uterine bleeding, radiation therapy is one of the most valuable because of the excellent results and the absence of mortality or morbidity.

*Carcinoma of the Cervix*

Carcinoma of the cervix is the most frequent malignant tumor of the female genital tract. Irradiation has one of its greatest fields of usefulness in this type of lesion. At the present time, there is a tendency to avoid accepted irradiation methods and to perform surgery. There is no doubt that surgery has a definite place in the therapy of carcinoma of the cervix in the very early lesions, with the carcinoma in situ or well localized. If the carcinoma is advanced, surgery becomes an extremely formidable procedure of doubtful value.

In recent years the earlier detection of carcinoma of the cervix has become possible with the vaginal smear,<sup>26</sup> and therefore treatment by either irradiation or surgery produces a much higher percentage of cures. Most patients, however, are first seen when the lesion is moderately advanced, and it is in these cases that irradiation is the treatment of choice. Anspach<sup>27</sup> states that in advanced lesions radical hysterectomy is a difficult procedure that can be performed only by a few highly trained and skillful gynecologists, whereas with irradiation there is practically no primary mortality and a minimum of morbidity. Irradiation can be used in the treatment of all carcinomas of the cervix regardless of their extent, with a large percentage of cures, in the earlier stages. It also effects good palliation in the very late stages, occasionally producing cures even in these cases. The results with supervoltage therapy in the advanced stages of the disease have not yet been fully evaluated.

Many methods of irradiation for carcinoma of the cervix have been advocated. The accepted procedure is to give intensive irradiation to the local lesion, usually by means of radium and protracted external x-radiation to the pelvis for disease in the parametrium. Most methods employ intrauterine and vaginal applicators. The intrauterine applicator is usually a tube containing several capsules of radium. The vaginal applicators include corks, plaques or colpostats containing radium capsules and placed against the cervix and in the lateral fornices. These provide effective intensive irradiation to the diseased cervix and parametrium.

Kaplan and Rosh<sup>28</sup> favor external irradiation followed by radium implantation and a subsequent course of external treatments. Elkins<sup>29</sup> and Bouslog<sup>30</sup> advocate intravaginal x-ray therapy combined with external therapy. Others<sup>31, 32</sup> use interstitial radium-needle implantation. Each method has its advantages.

Buschke and Cantril<sup>33</sup> do not follow a preconceived outline for treatment or a rigid technic. They write

Radiation therapy of cervical cancer has become one of the cornerstones of clinical radiation therapy. This supersedes surgery and is accepted as the superior procedure of choice because, in the overwhelming majority of cases, it accomplishes more with less risk if properly used.

## OVARY

There are many types of tumor of the ovary, both benign and malignant, but their classification is difficult because even today extremely little is known of their histogenesis. Mcigs<sup>11</sup> has outlined a classification according to the origin, whereas Cutler, Buschke and Cantrell<sup>12</sup> classify these tumors according to the type of proliferation. The malignant neoplasms are either solid or cystic. The latter are more frequent as well as relatively more radiosensitive than the former.

Most investigators agree that the proper treatment of carcinoma of the ovary is surgical extirpation of as much of the neoplastic tissue as possible, followed by an adequate course of radiation therapy. Kerr and Einstein<sup>13</sup> believe that postoperative irradiation should be given after the removal of as much neoplastic tissue as possible.

## SKIN

### Carcinoma

The local treatment of certain superficial skin diseases with radioactive phosphorus ( $P_{32}$ ) has been suggested by Low-Beer,<sup>14</sup> who soaked blotting paper in measured amounts of the solution and applied it to the skin surface, studying the effects of beta-particle radiation on the skin. Howes and Camiel,<sup>15</sup> Smathers<sup>16</sup> and others<sup>17,18</sup> discuss the value of low-voltage short-distance ("contact") x-ray therapy in the treatment of accessible superficial neoplasms. They believe that this method is of distinct advantage because the radiation is limited to the tumor and its immediate vicinity, the treatment time is short and the ultimate cosmetic result is excellent. Contact therapy is not applicable to bulky or inaccessible lesions. Strandqvist<sup>19</sup> and Ahlborn<sup>20</sup> have correlated the relation between total dosage and the treatment period and have charted the optimum tumor dosage for the desired number of divided doses over a given time. Hale and Holmes<sup>21</sup> compare the results obtained by the massive single-dose method and multiple treatments within the period of one week. They conclude that a dose of 2700 r given at one time produces essentially the same results as multiple doses totaling 4500 r delivered over a period of a week.

Warren<sup>22</sup> emphasizes the value of intensive therapy for skin cancer. He noted recurrences in the deeper layers, whereas the superficial portions healed with inadequate initial treatments. Young<sup>23</sup> points out that when recurrence follows either adequate or inadequate primary irradiation, radical surgical extirpation should be done.

## LYMPHOMAS

The experience of Reinhard et al.<sup>24</sup> at Washington University shows that radioactive phosphorus is ineffective for the lymphoma group of diseases. X-ray therapy is considered more desirable than

radioactive phosphorus and avoids the dangerous effects of that agent. Graff, Scott and Lawrence<sup>25</sup> made similar observations on experimental animals, demonstrating deleterious effects on the bone marrow and peripheral circulation with radioactive phosphorus. Any selective effect on tumor cells is greatly offset by the damage to the normal elements of the lymph and blood. The treatment of lymphomas is best carried out with x-rays at 200 kilovolts. The intensity and dosage vary according to the extent of treatment.<sup>26,27</sup> Desjardins<sup>28</sup> favors the use of moderately high voltages (around 140 kilovolts) and gives courses of treatment at intervals of several weeks.

When the disease is localized in a single small group of lymph nodes, the dosage should be in the range between 2000 and 3000 r.<sup>29</sup> Surgery has even been suggested for the freely movable, small mass of nodes.<sup>30</sup> Unfortunately, most patients are first seen in the advanced stages of the disease, when multiple groups of nodes are involved. When lymphoblastoma involves the spleen, mediastinum and lymph nodes, the treatment must be fitted to the individual patient. An acceptable rule is to give sufficient irradiation to cause complete regression of the nodes, with an additional 25 per cent for the residual microscopic tumor cells. This usually means a dose of 600 to 1800 r. Although larger doses can be administered, it is wiser to obtain a full effect with moderate doses. This procedure permits the administration of additional roentgenotherapy to the same areas later on when recurrences take place in other nodes. When a mass of nodes has been treated, incomplete disappearance does not mean failure of response. The replacement of disease by fibrosis often results in some residual enlargement. X-ray therapy is needless for enlarged fibrosed nodes and results in an expenditure of radiation that may be required in the event of future recurrence in the same regions. It must be recognized that the patient will become radioresistant, which usually indicates the terminal stages of the disease. Carefully planned irradiation often prolongs the period of radiosensitivity of the disease. The treatment of the acute forms of Hodgkin's disease is unsatisfactory at best. This consists of spray radiation or small amounts of irradiation over large surfaces of the body.

Nitrogen mustard has proved effective in isolated cases, but its use in routine therapy is considered unjustified.<sup>31</sup>

## PHARYNX, MOUTH AND SINUSES

### Larynx

The necessity of adequate cancerocidal doses for laryngeal carcinoma is stressed by Lenz,<sup>32</sup> who administers tumor doses varying from 5700 to 7000 r. In the presence of metastases to the lymph nodes, surgery is advocated when the nodes are freely movable. Otherwise, x-ray and radium are recom-



mended Arbuckle<sup>64</sup> states that the surgical removal of the thyroid cartilages allows large amounts of x-ray therapy to be given without danger of chondro-necrosis. Cutler<sup>65</sup> describes a method of concentrated radiotherapy, employed in the presence of radioresistant tumors of the larynx and pharynx. In this method the tumor is treated for a comparatively short time with large daily doses. This is in contrast to the Coutard method, in which small daily doses are given over a long period. Cutler<sup>66</sup> also diminishes the size of the field as treatment progresses, thus gaining the greatest concentration at the center of the tumor. The tumor doses vary from 5700 to 7700 r. The use of small fields, he states, is a definite advantage, allowing greater tumor doses with less effect on the surrounding normal tissues. This has also been pointed out by Blady and Chamberlain.<sup>67</sup>

The problem of surgery versus radiotherapy is discussed by Campbell,<sup>68</sup> who agrees that either form of treatment can be effective in the early stages of the disease. Radiation therapy is considered preferable in the early cases because the larynx is preserved, if proper and adequate radiation is given.<sup>66, 68</sup>

### *Nasopharynx*

Carcinoma of the nasopharynx is treated either by x-rays or a combination of x-rays and radium. Lenz<sup>69</sup> has shown five-year survival free of disease in 13 of 44 patients treated. It is interesting to note that 6 of these patients had lymphoepithelioma, which is an unusually radiosensitive tumor. Only 2 of these tumors were epitheliomas, slightly differentiated. Lenz considers the extent of disease and degree of bone involvement to be important factors in the prognosis. The presence of metastases is naturally of grave significance.

The use of radium therapy on lymphoid tissues of the nasopharynx was brought into prominence during World War II. The procedure was used successfully in the Air Forces to eradicate excess lymphoid tissues about the eustachian tubes.<sup>60-62</sup> Radium application and x-ray treatment of the lymphoid tissue of the nasopharynx are of value for deafness secondary to excess lymphoid tissues in the nasopharynx, infection of the middle ear and chronic otorrhea.<sup>63-65</sup>

### *Tongue*

Richards,<sup>66</sup> of Toronto, discusses radiotherapy in carcinoma of the tongue. He obtained three-year survival in 50 per cent of all cases treated. His treatment consists of external roentgen-ray therapy at 400 kilovolts, with a minimum tumor dose of 5500 r. When half the external dose has been given, intraoral radiation with 200 kilovolts is started and 3000 r is administered, so that the final tissue reaction is a summation of the external and intraoral irradiation. Residual carcinoma is

treated with interstitial radium, low-content (2-mg) needles being used.

### *Lip*

In carcinoma of the lip, the primary lesion may be controlled by irradiation or surgery, but the attack on metastatic lymph nodes in the neck is best carried out by radical dissection.<sup>67</sup> Routine prophylactic removal of the nodes is not recommended, but a careful follow-up study should be instituted. The early detection of nodes and prompt surgery give good results. When cervical metastases are too extensive for surgical removal, external irradiation together with radium seeds may be used. Schreiner and Christy<sup>68</sup> reported a series of 636 patients with cancer of the lip treated by x-rays or radium or both. They obtained an absolute cure rate of 58.9 per cent. The treatment of metastatic cervical lymph nodes by x-ray and radium therapy has been carried out with encouraging results by H. E. Martin<sup>69</sup> and C. L. Martin.<sup>70</sup>

### *Maxillary Sinuses*

Cancer of the maxillary sinuses still presents a challenge, because of failure to make an early diagnosis. Patients are often seen only after extension of the lesions into the surrounding bone structure. Valencia and Rosenthal<sup>71</sup> have accomplished eradication of epidermoid carcinoma in 2 of 3 cases reported, 1 patient surviving for three years and four months and the other for four years and two months.

### *MISCELLANEOUS CONDITIONS*

Munson and Munson<sup>72</sup> treated 20 patients with acute sinusitis with medium-voltage radiotherapy. Eleven patients had immediate relief after one treatment, and 4 after three treatments, 3 required five or six treatments. The authors conclude that small doses (100 to 150 r per treatment) give relief of pain in a large percentage of patients.

Roentgenotherapy in the atrophic arthritides relieves pain, spasm and stiffness according to Kuhns and Morrison.<sup>73</sup> Kersley,<sup>74</sup> writing of arthritis and rheumatism, asserts that probably no group of disease susceptible to x-radiation has been more neglected by the radiotherapist. Hemphill and Reeves<sup>75</sup> show that the best results in Marie-Strümpell disease can be expected if x-ray therapy is begun while there is still active granulation and before ankylosis has set in. They obtain reduction of pain and stiffness, gain in weight, decrease in sedimentation rate and a return to gainful occupation in a large proportion of patients.

Rapid and dramatic relief of the agonizing pain of acute bursitis has been demonstrated by Brewer and Zink,<sup>76</sup> who advocate a single large dose of 300 r with 200 kilovolt therapy. Others<sup>77, 78</sup> recommend smaller multiple doses. Only fair results have

been obtained with the chronic buristides, however, with relief reported in 30 to 40 per cent of cases 74-78

Robbins<sup>79</sup> demonstrated no ill effects and fairly long remission with multiple small doses to large areas of the body in the treatment of polycythemia vera. Hall et al<sup>80</sup> report their results with radioactive phosphorus in this disease. They observed remissions lasting from nine to twenty-six months. An excellent review of treatment results with radioactive phosphorus is presented by Reinhard and his co-workers.<sup>81</sup> The only encouraging results were found in the treatment of polycythemia vera. Other blood dyscrasias and lymphomas were more difficult to control than by roentgenotherapy.

In the treatment of acute infections, Kelly<sup>82</sup> points out that fairly large areas should be irradiated, including some normal tissue around the infection. He also notes that the sulfonamides alter or inhibit the effect of x-rays and points out that the two types of therapy should not be combined, since the combination of the therapeutic agents produces a high morbidity.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 34021

#### PRESENTATION OF CASE

A seventy-eight-year-old housewife entered the hospital with the chief complaint of difficulty in swallowing.

During the two years preceding admission the patient was bothered by a chronic nonproductive cough that went through cycles of exacerbation and remission. She denied hemoptysis and night sweats. About a year before admission she was put on a diet for hypertension and lost 20 pounds in five or six months. Following this, however, she continued to lose another 20 pounds, and lost her appetite. About three months before admission she became hoarse, the cough became coarse, and she noted weakness and fatigue. She had no difficulty in swallowing solid food, but liquids regurgitated into the nose. She denied nausea, vomiting, indigestion, abdominal pain or any abnormality of bowel habit.

Ten years before admission the patient had had a radical mastectomy for carcinoma simplex, with a metastasis to one of ten regional lymph nodes examined. Six years before admission a lymph node had been excised from the submaxillary region, and a diagnosis of malignant lymphoma, follicular type, was made. The patient had had known high blood pressure for many years and moderate dyspnea and orthopnea for several years. There was no edema of the ankles and no episodes of congestive failure.

Physical examination revealed a pale, obese, flabby, deaf woman in slight respiratory distress. The right breast was absent, and the operative wound was well healed, without evidence of recurrence. No lymph nodes were palpable in the neck or in the axillae. The chest was clear. The heart was questionably enlarged, with a Grade I apical diastolic murmur. The abdomen was soft, no organs or masses were palpable.

The temperature, pulse and respiratory rates were normal. The blood pressure was 220 systolic, 110 diastolic.

Examination of the blood disclosed a red-cell count of 4,300,000 with a hemoglobin of 14 gm, and a white-cell count of 7200, with 64 per cent neutrophils, 34 per cent large lymphocytes and 2 per cent monocytes. The nonprotein nitrogen, the total protein and the blood chloride were within normal limits. An electrocardiogram showed right bundle-branch block. An x-ray film of the chest revealed no abnormal shadows in the lungs, ribs or pleura. There was a streak of atelectasis in the right costophrenic angle. With the aid of a barium swallow a pressure defect was demonstrated in the esophagus, pushing it forward as well as narrowing the lumen. This was at the left of the aortic arch. A similar defect was demonstrated on the anterior margin just below the carina (Fig. 1).

On the fourth hospital day esophagoscopy was performed. An area of narrowing was found, but it was possible to pass the instrument beyond the point of obstruction and careful inspection showed no lesion of the mucosa.

X-ray therapy was begun, at first 200 and then 300 r to the mediastinum daily, followed by alternating anterior and posterior portals.

The patient did not do well. Cough, dyspnea and dysphagia continued. On the second day after esophagoscopy the temperature spiked to 101°F, and a chest film showed a markedly elevated right leaf of the diaphragm and several streaks of atelectasis about the dome. On the twenty-first hospital day a gastrostomy was done, but the patient was not benefited appreciably. The temperature from

the third postoperative day on was elevated, going as high as 102.6°F, and the operative wound broke down around the gastrostomy tube. The patient gradually lapsed into coma and died quietly on the eighth postoperative day. The chest had remained clear until the very end.

### DIFFERENTIAL DIAGNOSIS

**DR. CARROLL C. MILLER** We have two lines of attack in making the diagnosis in a case of this sort. The first is anatomic, to determine whether the mass that evidently accounts for the difficulty in swallowing was intraluminal, extraluminal or extrinsic to the esophagus. The other line concerns the relative probability of the three suggested pathological diagnoses—carcinoma of the esophagus, which, particularly in this age group, is most common, or metastasis from one of the malignant tumors already demonstrated, lymphoma or carcinoma of the breast.

May I see the x-ray films?

**DR. STANLEY M. WYMAN** The heart is prominent toward the left in the region of the left ventricle. The aortic arch is obviously tortuous, and there is tortuosity in the descending aorta, where it can be faintly seen behind the heart. There is a streak of atelectasis at the right base. Pressure on the esophagus is demonstrable on the right posterior aspect just below the level of the arch of the aorta in these two films and also on the spot film. A second area of pressure on the esophagus is seen lower down anteriorly on the left. These areas show no evidence of intrinsic involvement of the esophagus and appear to be pressing upon rather than arising in the esophagus.

**DR. MILLER** I assume that there is no fluoroscopic report to demonstrate motion of the right leaf of the diaphragm. The patient was perhaps too ill at this point to be fluoroscoped.

**DR. WYMAN** I believe that the patient was fluoroscoped, because of the spot films, but I do not know what the fluoroscopist said about the diaphragm.

**DR. MILLER** To go back to the first category, I think that we can dismiss an intraluminal growth as a cause of the obstruction. Two methods of examination are in agreement on this point: the swallow of barium revealed a clearly outlined mucosal pattern of the esophagus, and esophagoscopy showed no evidence of mucosal destruction.

So far as an intramural growth is concerned, we usually see a more definite bulging, a distortion of the mucosal pattern, and with it a mass of solid consistence outside the esophagus. But, again, it is not always definitely possible to see an intramural mass by x-ray examination.

Concerning the third group, the extrinsic masses, we can get only such information as the x-ray examination provided us with here. Usually, however, there are other data that help in making such

a decision, especially the presence of mediastinal lymph nodes. Dr. Wyman did not mention the presence of mediastinal nodes in these films. I do not see them, and I do not believe they are there.

**DR. WYMAN** I cannot identify them *per se*, unless the esophageal pressure defects are from enlarged lymph nodes.

**DR. MILLER** Before we discuss the more likely possibility one should mention other extrinsic causes for compression of the esophagus. The two more common ones are aneurysm and a benign



FIGURE 1

nontumorous obstruction from enlarged lymph nodes. I am thinking particularly of tuberculosis. We have had several cases of tuberculosis in this hospital with esophageal obstruction because of tuberculous involvement of mediastinal lymph nodes. I do not believe that this patient had an aneurysm; the x-ray studies do not show evidence of it. The symptom of hoarseness immediately makes one think of involvement of the recurrent laryngeal nerve, which is frequently seen with aneurysm. We do not know which nerve was involved. There was no mention of which cord was paralyzed. Because of the high diaphragm that subsequently developed I should guess that the right phrenic nerve became involved, and consequently paralysis of the right recurrent laryngeal nerve is more probable. I see no evidence of aneurysm of the right

subclavian artery or great vessels at the base of the heart

We have no further evidence of tuberculosis, although this is not necessarily required in making such a diagnosis. Cases of tuberculous adenitis may not have demonstrable evidence of tuberculosis in the chest or elsewhere. Having dismissed the most common causes of extrinsic pressure and having dismissed the diagnosis of epidermoid carcinoma of the esophagus, I might also dismiss adenocarcinoma of the esophagus because it is relatively rare to find adenoid tissue in the esophagus—at this level, particularly—not visible at esophagoscopy.

We can thus continue to a discussion of the likelihood of lymphoma or metastatic carcinoma, which brings us down to a more or less statistical discussion. The patient had had carcinoma of the breast ten years previously. Although the survival of patients with metastases from carcinoma of the breast is definitely short, in the region of 30 per cent five-year cures, we have been seeing what I would call a considerable number of late cases of metastatic carcinoma from the breast anywhere from six to twelve years postoperatively. These patients have no symptoms whatsoever of metastatic disease. In reference to the exact symptoms that this patient had, we find a common one, frequently the first that bothers the patient with this disease—namely, cough. For two years she had had non-productive cough, evidently a general irritative phenomenon around either the trachea or major bronchi. The x-ray studies in this hospital showed no evidence of pulmonary disease in this patient. We must assume that she had a more local irritative factor. These patients who first begin to cough years after a radical mastectomy for carcinoma have a nonproductive cough, and they have increasing dyspnea as the mediastinal lymph nodes encroach more and more on the major bronchial system. Subsequently, they have collapse of various parts of the lung because of unsatisfactory drainage from the bronchial tree. So much for carcinoma. Another red herring is the presence of malignant lymphoma in this history—one solitary focus removed six years previously from the submaxillary gland. Do we know if she ever had evidence of recurrence of this tumor?

DR TRACY B MALLORY The patient was followed at relatively frequent intervals at the Huntington Clinic, and no evidence of recurrent disease was found.

DR MILLER It is said that malignant lymphoma may remain quiescent for many years. One author quotes the average duration of life with malignant lymphoma of the follicular type as four years, but various others list it as six to fourteen years. The diversity of lymphomatous involvement in the body is well known, and there may be such disease in the mediastinal nodes to account for this difficulty.

I believe that I must make a diagnosis of metastatic carcinoma of the breast. The patient had progressive weight loss. This is frequently found in the absence of symptoms or definite physical demonstration of metastatic disease. She had an invasive type of tumor. I say that because she must have had nerve palsy of both the recurrent laryngeal nerve and the phrenic nerve. She had progressive disturbance of the esophagus and the bronchial system, with increasing dysphagia and increasing tracheobronchial irritation. The difficulty in swallowing liquids, with no difficulty in swallowing solid food, is also suggestive of nerve injury.

DR MALLORY Would anyone care to consider the possibility of primary bronchiogenic carcinoma?

DR DONALD S KING I do not see how it could be ruled out.

DR MILLER Certainly the sequence of events is compatible with that diagnosis. Multiple malignant tumors in the same patient are being more and more frequently seen. This patient would then have had three different tumors.

#### CLINICAL DIAGNOSIS

Metastatic carcinoma of mediastinal lymph nodes

#### DR MILLER'S DIAGNOSIS

Metastatic carcinoma from breast to mediastinal lymph nodes, involving esophagus and right main bronchus

#### ANATOMICAL DIAGNOSES

(Carcinoma of breast)

*Metastases to mediastinal lymph nodes involving esophagus and right main bronchus*

Metastases to liver

#### PATHOLOGICAL DISCUSSION

DR MALLORY The section from the submaxillary region on which the diagnosis of giant follicular lymphoma was made a few years ago was shown to me before I knew the history and the outcome of this case, and I disagreed with the diagnosis, reporting it as inflammatory hyperplasia. At autopsy we found a very scirrhous tumor occupying the region of the mediastinal lymph nodes, which were largely unrecognizable. The tumor had extended posteriorly into the wall of the esophagus and anteriorly into the wall of the right bronchus. There was extensive involvement of the bronchial mucosa. Therefore, from the gross evidence it could have been primary bronchiogenic carcinoma. We believed that we could rule out a primary tumor of the esophagus.

Microscopical sections showed a scirrhous adenocarcinoma, and though not absolutely conclusive were much more suggestive of a metastatic lesion from the breast than of a primary bronchial tumor. Part of the swallowing difficulty was due to a retropleural abscess above the point of tumor involvement of the esophagus. There were some

metastatic nodules in the liver. There was no evidence of lymphoma at autopsy.

DR. MILLER: What do you suppose the duration of the abscess was?

DR. MALLORY: A number of days or perhaps a couple of weeks — a very acute lesion, I believe.

## CASE 34022

### PRESENTATION OF CASE

A fifty-one-year-old Italian electrical worker was admitted to the hospital because of hemoptysis.

Two years previously, he had an upper respiratory illness characterized by cough, sweating and pain in the right lower portion of the chest on breathing. He had not worked for several weeks, but did not remain in bed. Recovery from this episode was apparently complete, but eight months later a similar episode occurred. At that time the cough was productive of considerable whitish sputum. A bronchoscopy was performed, but no diagnosis was given to the patient. Three months before entry, he again began to feel "bad all over." The cough returned, persisting throughout the day, and was productive of a small amount of blood-tinged sputum, which was raised mainly in the mornings. He had been anorexic, with a weight loss of 7 pounds, and had been unable to work for three months.

Physical examination revealed that the lower third of the right portion of the chest posteriorly was dull to percussion, with diminished breath sounds heard over the area. The prostate was regular, firm and enlarged to twice the normal size.

The temperature, pulse and respirations were normal. The blood pressure was 125 systolic, 80 diastolic.

Examination of the blood disclosed a hemoglobin of 14.6 gm and a white-cell count of 10,600, with 71 per cent neutrophils, urinalysis was negative. A blood Hinton test was negative. Five sputum examinations and one guinea-pig inoculation were negative for tuberculosis.

An x-ray film of the chest showed a segmental area of atelectasis posteromedially in the right lower lobe. The adjacent portions of the lower lobe close to the abnormal area were somewhat emphysematous. There were small blebs in both apices. The heart was displaced slightly to the right. A bronchogram revealed incomplete visualization of the right middle-lobe bronchus, and the middle lobe appeared slightly diminished in size. The bronchi to the anterior basal segment and dorsal division of the right lower lobe appeared normal, the bronchi leading to the atelectatic area were not filled. Laryngoscopy and bronchoscopy disclosed considerable thick yellowish-green secretion in the larynx and trachea. The right bronchial tree was reddened throughout and contained thick yellowish-green secretion. The

right upper-lobe orifice was reddened, and the bronchus displaced downward. The stem bronchus and the middle-lobe orifice were also reddened. The lower-lobe bronchus was red, edematous and displaced to the right, with considerable thick secretion and edema. No adenoma or foreign body was visible. The remainder of the examination was negative.

On the fourteenth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. LAMAR SOUTTER: The general picture is that of a middle-aged electrical worker with a brief history of pulmonary disease — that is, brief compared to many stories of chronic pulmonary infection that we see. There were three episodes of illness: one, two years before entry, one fourteen months before entry, and finally a third. The first two illnesses were not of very long duration, and recovery was apparently quite complete. They seemed to be infectious in nature. I do not receive the impression of a patient with steadily progressive disease, such as might be expected with tumor, but rather a picture of two attacks of pneumonitis with sputum, and probably an elevated temperature, although that is not stated. He did have pain in the right lower portion of the chest, and hemoptysis, on one occasion. The third sickness was of much longer and more serious extent. The patient when he came in had been unable to work for three months. On arrival at the hospital he gave the appearance of having chronic pulmonary infection. He did not have a high temperature, although he had a slight elevation of the white-cell count. He was raising sputum, and he had morning sweats, malaise, anorexia and weight loss.

What would be the source of a chronic infection in a man of this age coming into the hospital with this brief history? In looking back on the first two episodes, the possibility of septic infarction arises, followed by abscess formation, the abscess healing but perhaps breaking down and healing and breaking down again. On the other hand one wonders about that when presented with the x-ray picture showing an area of increased density without the fluid level that one might expect in an abscess of some two years' standing, which had been active for at least three months prior to entry. We do have the idea, however, that although an abscess was unlikely there was probably some bronchial obstruction because atelectasis was observed by x-ray examination.

I wonder if Dr. Wyman will show the x-ray films at this point?

DR. STANLEY M. WYMAN: The only available films are those taken after the introduction of lipiodol. The left anterior oblique view shows best the area of atelectasis, in the posterior medial

segment of the right lower lobe. The bronchi to this region are incompletely filled.

DR SOUTTER: Does the incomplete filling suggest difficulty in injecting the dye or an obstruction of the bronchi?

DR WYMAN: There is some obstruction of the flow of lipiodol to that region. I can see no definitely abnormal bronchi on the right side. The left side appears perfectly normal.

DR SOUTTER: The information that is given to us by the x-ray pictures is one of atelectasis with possible partial obstruction to the bronchus leading to the atelectatic area. It is probably right to assume that the chronic infection had its origin in this collapsed area. What should we regard as the etiology of this collapse? Obstruction, partial or complete, in a bronchus can come from extrinsic pressure, from cicatricial narrowing of the bronchus secondary to infection or from obstruction inside the bronchus by a mucous plug, by a foreign body, by an adenoma or by a carcinoma.

What information do we get from bronchoscopy? It confirmed the evidence of infection in the right side of the lung. The sputum was described as thick and greenish, it was not described as foul. We can assume that the aspirated secretion came from the right lower lobe by the description of edema in this bronchus. The reddening elsewhere reflects the severity of the infection rather than an extension of the disease process.

DR EDWARD B. BENEDICT: In the bronchoscopic report I mentioned that the breath was very foul.

DR SOUTTER: There is some evidence, then, of a possible putrid abscess, since the breath was foul, and that is something that we should consider.

What about infection causing obstruction of the bronchus? The x-ray picture is not one of a true bronchiectasis due to a mixed infection. We do not have a report of the sputum culture. We cannot tell, of course, whether the lipiodol failed to enter the bronchus or whether there was some bronchiectatic obstruction. This is not the typical picture of long-standing pulmonary infection or the characteristic story of bronchiectasis that goes back to childhood. If present from childhood the disease is usually manifested at an earlier age. So we may assume that whatever caused the trouble was probably more recent, and that bronchiectasis on the basis of chronic infection is probably not a great likelihood in this case.

What about bronchiectasis on the basis of tuberculosis? Has that been completely eliminated by the sputum studies or the location of the atelectasis? I do not believe that it has been completely eliminated. With the report of thick, greenish, foul sputum, which was negative on bacteriologic study, however, it is probably not very likely.

We should consider actinomycosis, blastomycosis or some fungous infection. The position is right for abscess formation due to these types of organisms.

These abscesses are usually in the lower lobes when they occur. On the other hand, the causative organisms are generally readily identifiable by sputum examination. In actinomycosis the sulfur granules are often coughed up. We have seen an occasional case in which these organisms did not appear in the sputum, and not until after the lung tissue had been removed was it obvious that actinomycotic abscess was the correct diagnosis.

What about the possibility of a foreign body plugging the bronchus? That is not likely in an adult without a history of aspirating some object. In a child such a diagnosis could be seriously considered without such a history, but not in an adult. Furthermore, we might see a radiopaque foreign body by x-ray study.

That brings us, then, to the consideration of whether or not this could have been a tumor of some sort. We think first of course of an adenoma—or, in other words, a benign tumor arising in a bronchus. Most adenomas arise in the main bronchus on one side or in a branch of it. Very seldom do they occur so far peripherally as not to be readily observed by bronchoscopy. They usually occur in people younger than this man. The patient nearly always gives a history of chronic infection or hemoptysis before coming into the hospital.

Could this have been a metastatic carcinoma? A metastatic carcinoma usually appears as a round shadow in the lung periphery. It will not cause collapse of a lung segment until it has grown large enough to press on a bronchus. The only organ suggested by the story as a source of a primary tumor was the prostate. Although the prostate was enlarged to twice the normal size, it was smooth and not nodular. Furthermore, the history was not that of metastatic disease.

Other diseases such as sarcoid and lymphoma should be mentioned. They seem unlikely because in those diseases the lesions are usually multiple and give a different x-ray appearance, atelectasis being more apt to occur very late as they progress.

Therefore we come down to bronchiogenic carcinoma. Adenocarcinoma is less common than the epidermoid type. What is the possibility of an epidermoid carcinoma with partial or complete bronchial obstruction, dilatation of the bronchus distal to this with abscesses and a great deal of inflammation? I think that the chances are very good. The patient was in the right age group for cancer although younger than many patients with bronchiogenic carcinoma whom we see. This tumor does not always occur at the hilus. It can occur in bronchial tissue far out in the periphery of the lung. It is nearly always attended by atelectasis—so much so that I feel strongly that atelectasis in a patient in this age group, without evidence of other causative disease, should be regarded as secondary to bronchiogenic carcinoma. What about the emphysematous blebs and the bloody sputum?

I do not believe that the blebs were of any importance in this man. Blood-tinged sputum can occur in a great number of diseases and is not of much help diagnostically.

I shall hazard a diagnosis of carcinoma of the bronchus leading to the collapsed area of the lung and atelectasis, with chronic infection and perhaps small abscesses in that segment of the lung.

DR. DONALD S. KING: I cannot remember any case with cancer in a bronchus with a negative bronchoscopy, can you, Dr. Benedict?

DR. BENEDICT: No, I cannot, and my impression was that the bronchoscopy was definitely consistent with bronchiectasis—that is, a hemorrhagic bronchiectasis with a red, edematous mucosa that we frequently see in straight bronchiectasis causing enough bronchial obstruction to give this picture.

DR. KING: That would be my bet. I was trying to think whether this was one of Dr. Sweet's pneumonitis cases and whether one would find cholesterol. I would bet that it was not that type of disease, but an area of bronchiectasis with abscess, which usually does not give so much cholesterol as these so-called pneumonitis cases. We have not a plain x-ray film to see if the abscess looked as much like tumor as those in Dr. Sweet's cases did.

DR. JOHN G. SCANNELL: This man had had a previous bronchogram six to eight months prior to entry here that showed diffuse bronchiectasis of the right lower lobe and also questionable involvement of the right middle lobe. We repeated this for our own information partially, and our feeling was that he had bronchiectasis in the major portion of the lower lobe. It improved for a period as judged by x-ray study, but we were puzzled by the segmental nature of the process. We debated whether or not to let the patient go home and get the bronchus in better shape and come back for a surgical procedure. In view of the segmental nature, Dr. Churchill thought that we should proceed with operation. With the data we had and with a man in this age group a lobectomy was done (Fig. 1). The pleura as I remember it was involved. The lobectomy was carried out without undue difficulty. The gross appearance of the lung was that of recurrent infection. The lower lobe showed the gross appearance of bronchiectasis. We did not open the bronchi at operation.

#### CLINICAL DIAGNOSIS

Bronchiectasis, right lower lobe

#### DR. SOUTTER'S DIAGNOSES

Epidermoid carcinoma of branch of right lower-lobe bronchus  
Secondary atelectasis and infection

#### ANATOMICAL DIAGNOSES

*Epidermoid carcinoma of bronchus of right lower lobe*  
*Bronchiectasis*  
*Pneumonitis, chronic*

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: When the lung was sectioned in the laboratory we found the bronchi-



FIGURE 1

ectasis, but it was obvious that there was also slight but definite nodularity of the mucous membrane of the bronchus. Sections from that area showed an epidermoid carcinoma. The surrounding lung tissue showed chronic pneumonitis of the secondary suppurative type seen with bronchiectasis.



segment of the right lower lobe. The bronchi to this region are incompletely filled.

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for the detection of tuberculosis, may well turn out to be of the greatest value as a public-health measure in the control of cancer

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#### EATING OUT IN SAFETY

AN ARTICLE in the Massachusetts Department of Public Health column in this issue of the *Journal* gives information that makes us wonder why even more illness does not result from the increasing American custom of eating out, for surveys conducted by the Massachusetts Department of Public Health during the last two years disclose that the sanitary conditions in restaurants and other eating places in the Commonwealth are far from ideal.

Public opinion, apparently, is doing a very satisfactory job of policing the conditions in the front of such establishments, and places that do not provide clean and cheerful surroundings fail to gain patronage. Unfortunately, the public usually knows very little of what is going on behind the scenes, where the danger usually lurks, and in communities where there are no regular inspections by health-department personnel slipshod methods quickly develop.

The public, however, has the right to expect that health agencies will take the responsibility for seeing that what happens behind the scenes is not endangering health, on the other hand, the health agency can expect the community to provide sufficient well trained personnel so that this responsibility can be satisfactorily met. In many municipalities the remuneration available for health-department employees is not sufficient to obtain

the services of an inspector who knows enough about restaurant sanitation to do a satisfactory inspection job. The Massachusetts Department of Public Health with its small staff of sanitarians can only attempt to assist local inspectors in learning to make satisfactory inspections so that owners of eating places may be informed of what is expected of them.

It is not surprising that some of the conditions exist because even owners have had little opportunity to learn the importance of many of the procedures usually demanded in restaurant sanitation regulations. Owners are usually co-operative in improving conditions when the faults are called to their attention.

Physicians, as important citizens of the community, can exert a forceful influence on this particular problem if they will inform themselves regarding conditions in their own communities and speak a word to the proper public officials.

#### MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

##### RESTAURANT SANITATION

Hardly a week goes by in Massachusetts that we do not hear of an outbreak of disease following a church, school or lodge banquet, or a meal served at some large cafeteria or a restaurant. Unfortunately, most of the outbreaks due to contaminated food in restaurants are never officially reported. That such outbreaks do originate in restaurants is evidenced by the fact that various members of the Department bear about them, sometimes weeks or even months after they occur.

Most outbreaks could be prevented if three important items of sanitation were strictly observed: if persons handling food took more interest in personal hygiene, and particularly if they kept their hands clean, if all foods favorable to the growth of bacteria were properly refrigerated, and if multi-use utensils employed in the preparation or serving of food and drink were thoroughly cleaned and effectively sanitized immediately after the day's operation, or more frequently if necessary.

Other items of sanitation such as cleaning and bactericidal treatment of eating and drinking facilities, structural facilities and waste disposal are important, but the experience in Massachusetts is that the three items mentioned above are the most important ones.

The Department of Public Health, through the Division of Food and Drugs, has authority to in-

ment (this has several advantages — it helps to make a large enough population unit to make a department economically possible and efficient and tends to equalize the differences in wealth between urban and rural areas, and the city, which depends upon its surrounding rural areas for much of its wealth and trade, should thus also be prepared to co-operate in providing basic health services required in common by all the people of the composite community), and in counties with less than 50,000 population, two or more that form a natural trade and transportation area should pool their resources to form a district health unit with at least this minimum population — more adequate services for the same amount of per capita expenditures can be achieved with an even larger population than the minimum, such as 100,000 or more, if no part of the population of the area is more than forty miles from the central point at which the health department would be located

The following seven steps are necessary to build a community temple of health the state health department should have a workable plan whereby local health service can be carried out for every community in the state, a state-wide citizens' health committee that includes representatives of voluntary and citizen agencies and that is approved by the governor should be organized, if it does not already exist there should be clear-cut legislation providing for county, city-county or district boards of health, the legislation should include authorization for personnel and salaries, the legislation should also include specific authorization for tax support of the local health department, and there should be agreement among state and local authorities concerning local, state and federal sources of tax support, a program of recruiting and training personnel, including in-service training, must be carried out, and a local community council must follow through to obtain local tax support and to keep the department alert, once it is organized

LOCATION OF TUMOR DIAGNOSTIC SERVICE

As announced in an earlier issue of the *Journal*, the Diagnostic Laboratory of the Massachusetts Department of Public Health is now located at 281 South Street, Jamaica Plain, with the Wassermann Laboratory (JA 4-1232) on the first floor and the Bacteriological Laboratory (JA 4-5440) on the second floor

Misunderstandings, however, have apparently occurred regarding the location of the Tumor Diagnostic Service This service is still located at the Harvard Medical School, 25 Shattuck Street,

Boston (LO 6-2380) The outfits for shipping specimens, however, are still to be ordered from the Diagnostic Laboratory, 281 South Street, Jamaica Plain

MISCELLANY

BORDEN AWARD

The American Academy of Pediatrics recently announced that the Borden Award for "outstanding research in the nutrition of infants and children" has been given to Dr Grover F Powers, chairman of the Department of Pediatrics at Yale University School of Medicine. The award, which is administered by seven professional and scientific associations, was established in 1936 to recognize and encourage outstanding research achievements in the food industry and related fields

Dr Powers is president of the American Pediatric Society and a former president of the New England Pediatric Society

AMERICAN HOSPITAL ASSOCIATION

Eighteen institutes for hospital administrative personnel, offering intensive hospital service education in short courses, have been scheduled for 1948 by the American Hospital Association Designed to provide basic material and information, together with a discussion of current problems, the institutes will feature authoritative faculties and are located so that hospitals in all parts of the country may participate Further information on the institute schedule will shortly be made available to Association members in a special brochure

In addition to the following, tentative plans have been made for an institute on pharmacy in May in the East, a November institute on hospital purchasing, also in the East, and a Middle Western institute on nurse anesthetists in December

DATE	PLACE	CITY	SUBJECT
January 12-16	Soreoo Hotel	St Petersburg Florida	Dietetics
January 26-30	Wisconsin Hotel	Milwaukee Wisconsin	Medical records
February 23-25*	Grady Hotel	Atlanta, Georgia	Personnel
March 1-5	Drake Hotel	Chicago Illinois	Nursing
March 8-12	Providence Hospital Auditorium	Oakland, California	Nurse anesthetists
April 12-13*	Continental Hotel	Kansas City, Missouri	Dietetics
April 26-30	Drake Hotel	Chicago Illinois	Housekeeping
April 19-23	Buck Hill Falls Inn	Buck Hill Falls, Pennsylvania	Dietetics
May 17-21	Shirley Savoy Hotel	Denver, Colorado	Purchasing
May 24-28	Knickerbocker Hotel	Chicago, Illinois	Operating engineers
May 31-June 4	Westminster Choir College	Princeton New Jersey	Public relations
June 8-12	Duke Hospital	Durham North Carolina	Medical records
July 19-23	Penn Sheraton Hotel	Philadelphia, Pennsylvania	Laundry
July 26-30	Drake Hotel	Chicago, Illinois	Accounting
October 4-8	Hotel New Yorker	New York City	Personnel
November 15-19	Wiltroo Hotel and Municipal Auditorium	Long Beach, California	Accounting
December 6-8*	Roosevelt Hotel	New Orleans, Louisiana	Public relations
December 6-10	Wardman Park Hotel	Washington, D C	Hospital planning

\*Short institutes.

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC

At the annual meeting of The American Society of Anesthesiologists held in New York City on December 4, 5, and 6, 1947, John Abajian, M D, of the University of Vermont College of Medicine, Burlington, Vermont, was elected to the Board of Directors of that society

## BOOK REVIEWS

*Osteotomy of the Long Bones* By Henry Milch M.D. 8<sup>th</sup>, cloth, 294 pp with 181 illustrations. Springfield Illinois Charles C Thomas 1947 \$6.75

Dr. Milch, after long study and experience, has changed the so-considered simple osteotomy to a surgical procedure of refinement and mathematical exactness. The various types of osteotomy, local, torsional, transpositional and angulation, are discussed. He shows how varying lengthening and shortening can be obtained by placing the osteotomy site higher up or lower down upon the shaft of the bone and also by varying the amount of angulation at the osteotomy. This can be figured readily by trigonometric formulas. In the femur the greatest increase in length is accomplished by complete valgus of the femoral neck. For the solution of these complex problems about the head and neck of the femur the author has devised a movable frame to show movement of the pelvis and femur and the length of the weight bearing line after osteotomy and abduction. This frame he calls an "osteometer". He discusses the application of osteotomy to ununited fractures of the femoral neck, osteoarthritis and tuberculosis. He should be commended for giving so clear and sensible a discussion of osteotomy. Every orthopedic surgeon will profit from reading this book.

*Textbook of the Nervous System. A foundation for clinical neurology.* By H. Chandler Elliott M.A. Ph.D. With an introduction by Wilder Penfield M.D. 4<sup>th</sup>, cloth 384 pp with 158 illustrations and an atlas. Philadelphia J. B. Lippincott Company 1947 \$8.00

This anatomic study of the nervous system incorporates a number of new principles, all of them of distinctive importance. To acquaint the medical student with the complicated anatomy of the whole nervous system the author has divided the book into two parts. The first which contains a simple outline covers about a hundred pages, giving the essentials and is illustrated with diagrams often printed in two colors the field covered is that needed by every medical student. In the second part, the anatomy and the more simple function of the nervous system are taken up in more detail, corresponding to the needs of an advanced student or one who is going to practice clinical neurology. With the details of the gross anatomy are many diagrams illustrating the text. These are line drawings, giving so extremely clear concept of structural anatomy particularly of the brain. They are by far the best diagrams known to the reviewer, accompanying them is a text of equal value. In addition, the author has provided, in the appendixes a list of the principal terms used in anatomy making particularly clear those of Latin and Greek derivation. A bibliography adds to the value of the work, and by a system of single and double stars papers and books of particular importance are emphasized. Furthermore the book is accompanied by an atlas showing the actual appearance of the brain as the result of a surgical operation, the major details of the skull and serial sections through the principal areas of the brain. There is an excellent index. The book deserves the highest recommendation. It is finely printed on excellent paper and both the publisher and the author ought to be congratulated on producing an epoch-making contribution to the medical literature.

*Hospital Care in the United States. A study of the function of the general hospital. Its role in the care of all types of illness and the conduct of activities related to patient service with recommendations for its extension and integration for more adequate care of the American public.* 8<sup>th</sup>, cloth 631 pp., with 94 tables and 58 charts. New York The Commonwealth Fund, 1947 \$4.50

In 1932 the Committee on the Costs of Medical Care presented the first comprehensive study of sickness, health and hospitals in the United States considered the problem of sickness, treatment and prevention as well as the extent of availability and use of medical care. The report computed its cost to the patient and income to the physician. It presented the needs of the country in doctors and hospital beds separating the cost of sickness into hospital and nursing expenses, charges for medicines and professional fees. It

clearly established the importance of hospitals in the medical structure.

The report of the Commission on Hospital Care further emphasizes the strategic position of the hospital by devoting its entire 600 pages to a discussion of the function of the general hospital in the care of all types of illness. The study also discusses patient service and makes recommendations for its extension and integration for more adequate care.

The Commission consisted of twenty-two persons in addition to a study staff of nine members and eight technical advisers, assembled in 1944 by a post-war planning committee appointed by the trustees of the American Hospital Association. It was financed by The Commonwealth Fund, the W. W. Kellogg Foundation and the National Foundation for Infantile Paralysis. Although the work antedated and was separate from the surveys authorized by the Hospital Survey and Construction Act, its activities undoubtedly influenced the Congress and advanced surveys in the states. The report is presented "to the American people as a guide to the future development of hospital care and as such commends itself to all serious students of medical and hospital problems."

The one hundred and eighty-one conclusions and recommendations presented in the second chapter appear overwhelming until it is realized that this section summarizes the wide variety of subjects covered in detail in the next three hundred pages.

Section III lays a foundation of facts and information dealing with a diversity of subjects including factors that have influenced the growth of hospitals, such as religion and war, the growth of hospitals in the United States, the functions of a general hospital, its relations with public health departments and standards of service and financing.

The following sections present new and original data regarding the size and need of hospital facilities such as population vital indexes, socioeconomic conditions, geography and transportation, the relation of bed-occupancy rate to size of hospital, the effect of urban or rural surroundings, and finally a formula for measuring the need of a community for hospital facilities by means of the ratio of beds to deaths.

It has been found that the public uses two hundred and fifty days of general hospital care for each death and correlated sickness cared for in a general hospital. On an annual basis adjustment of this figure gives 0.7 bed for each hospital death (bed-death ratio). This ratio must be adjusted again to allow for a normal occupancy of 75 per cent, or 0.875 beds. The death rate in the nation is 10.6 per 1000. The Commission assumed that half these might properly be expected to occur in hospitals or 5.3. Consequently 5 beds was computed as the number of general hospital and allied special-hospital beds per 1000 population as the ultimate and ideal future need of the nation.

There are many methods of computing hospital-bed needs but the Commission recommends this as the most reliable, pointing out that it is applicable under varying conditions of urban and rural areas, in districts of both low and high incomes and in other economic or population conditions and that it expresses accurately the ratio of actual use as well as the anticipated immediate needs and can also be used to foretell future needs. For example, when hospital deaths are 4.0 per 1000 occupied beds are 2.8 per 1000 population. As hospital deaths increase so should the number of beds available be increased up to the assumed maximum of 5 beds per 1000 population.

These three hundred pages are the heart of the report and represent the constructive work of the Commission. The final two hundred pages present the best history of hospital development in the United States yet compiled and one to which reference will be gratefully made for years to come.

The final chapter presents a useful listing of all the governmental departments and agencies with which hospital administrators have to deal.

In short, this is primarily a reference book of great value for the planning of hospital development, illustrated with well explained charts and tables graphically showing the wide variation of hospital facilities and services in the different states. A practical yardstick for measuring hospital bed needs in the bed-death ratio, and future development and expansion for both urban and rural communities is intelligently discussed. Finally there is an interesting and instructive history of hospital development in the United States.

## NOTICES

## ANNOUNCEMENTS

Dr Robert L. Cook announces the removal of his office to 38 Russell Park, Quincy

Dr Edward H. Hommel announces the removal of his office to 196 Dorchester Street, South Boston

Dr Samuel B. Kirkwood announces the removal of his office for the practice of obstetrics and gynecology to 1180 Beacon Street, Brookline

Dr Samuel Orlov announces the removal of his office for the practice of general medicine to 10 Reland Street, Middleboro

Dr Philip E. A. Sheridan announces the removal of his office to 80 Bay State Road, Boston

Drs Jacob H. Swartz and Earl A. Glicklich announce the removal of their office to 422 Beacon Street, Boston, for the practice of skin diseases

## BOSTON MEDICAL HISTORY CLUB

A meeting of the Boston Medical History Club will be held in Sprague Hall, Boston Medical Library, 8 Fenway, on Monday, January 12, at 8 15 p.m. I. Bernard Cohen, Ph.D., instructor in the history of science and general education, Harvard University, and managing editor of *Isis*, will speak on the subject "Some Scientific and Medical Aspects of Benjamin Franklin in Relation to Medicine and Science."

All interested persons are cordially invited to attend

## NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held at the Peter Bent Brigham Hospital, Boston, on Monday, January 26, at 8 15 p.m., with Dr. Samuel A. Levine presiding

## PROGRAM

Auscultatory Findings in Auricular Flutter Drs W. Proctor Harvey and Samuel A. Levine.  
Studies on Cardiac Tamponade Drs H. Hellems, J. M. Evans and Lewis Dexter  
Present Status of Surgical Treatment of Coarctation of the Aorta Dr Robert E. Gross  
Wolff-Parkinson-White Syndrome and Myocardial Infarction with Demonstration of Anomalous Bundle Drs Harold D. Levine and J. C. Burge, Jr.  
Physiological Studies on Eisenmenger's Complex Drs James Dow, Eugene C. Eppinger and C. Sidney Burwell  
A Neglected Form of Reversible Heart Failure Drs Edward Phillips and Samuel A. Levine

Interested physicians and medical students are cordially invited to attend

## NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Tuesday, January 27, at 8 p.m. A panel discussion on bleeding from the alimentary tract will be led by Dr. Arthur W. Allen, assisted by Drs. Franklin W. White, Richard B. Cattell, Thomas H. Lanman and Robert R. Linton, followed by a period of questions from the floor. A collation will be served. All physicians are invited.

## ELLA SACHS PLOTZ FOUNDATION FOR THE ADVANCEMENT OF SCIENTIFIC INVESTIGATION

During the twenty-fourth year of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation,

fifty-two applications for grants were received by the Trustees, twenty-one of which came from the United States, the other thirty-one coming from thirteen different countries in Europe, Asia and North and South America. Twenty-six grants were distributed.

Applications for grants to be held during the year 1948-1949 must be in the hands of the Executive Committee before April 15, 1948. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance and what other sources of support are relied on for research. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only applicants complying with the above conditions will be considered. Applications should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston 14.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 15

## FRIDAY, JANUARY 16

\*9:00-10:00 a.m. Diagnosis of Thyroid Deficiency and the Use of Thyroid Hormone Therapy in Infants, Children and Adolescents. Dr. Nathan B. Talbot. Joseph H. Pratt Diagnostic Hospital.

\*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

## MONDAY, JANUARY 19

\*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

## TUESDAY, JANUARY 20

12:00 p.m. X-Ray Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

\*12:15-1:15 p.m. Clinicorontgenological Conference. Peter Bent Brigham Hospital.

## WEDNESDAY, JANUARY 21

\*9:00-10:00 a.m. Recurrent Spontaneous Pneumothoraces and Their Surgical Treatment. Dr. Francis M. Woods. Joseph H. Pratt Diagnostic Hospital.

\*12:00 p.m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

\*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

\*Open to the medical profession

JANUARY-APRIL Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

JANUARY 12 Boston Medical History Club. Notice above.

JANUARY 13 New England Society of Anesthesiologists. Page 36, issue of January 1.

JANUARY 13 Harvard Medical Society. Page 36, issue of January 1.

JANUARY 14 Phi Delta Epsilon Lecture. Page 968, issue of December 18.

JANUARY 20 AND 21 American College of Surgeons. Commodore Perry Hotel, Toledo, Ohio. Page 930, issue of December 11.

JANUARY 26 New England Heart Association. Notice above.

JANUARY 26 AND 27 American College of Surgeons. Ansley Hotel, Atlanta, Georgia. Page 930, issue of December 11.

JANUARY 27 Norfolk District Medical Society. Notice above.

JANUARY 30 AND 31 American College of Surgeons. Oklahoma Biltmore Hotel, Oklahoma City. Page 930, issue of December 11.

JANUARY 30 AND 31 Conference on Normal and Pathologic Physiology of Pregnancy. Page 1004, issue of December 25.

FEBRUARY 6 American Board of Obstetrics and Gynecology. Page 36, issue of January 1.

FEBRUARY 12 Slipping of Upper Femoral Epiphysis. Dr. John A. Reidy. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 23-28 Postgraduate Assembly in Endocrinology. Page 36, issue of January 1.

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston.

APRIL 19-23 American College of Physicians. Page xiii, issue of July 31.

MAY 6-8 American Association for the Study of Goiter. Page xiii, issue of July 31.

(Notices continued on page xv)

## NOTICES (Continued from page 72)

May 17-20. American Urological Association Hotel Statler Boston.  
 May 18-22. American Association on Mental Deficiency Copley Plaza Hotel Boston  
 May 25-27. Massachusetts Medical Society Annual Meeting Hotel Statler Boston.  
 July 12-17. First International Poliomyelitis Conference Page 36, issue of January 1

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

JANUARY 13  
 MARCH 9  
 MAY 11. Annual Meeting. Hotel Weldon  
 All other meetings will be held at the Franklin County Hospital.

## MIDDLESEX EAST

JANUARY 21  
 MARCH 24  
 MAY 12. Annual Meeting  
 All meetings will be held at the Bear Hill Golf Club

## WORFOLK

JANUARY 27 Round-Table Discussion: Bleeding from the alimentary tract.  
 FEBRUARY 24. Obstetric and Gynecologic Night  
 MARCH 23. Harvard Night.

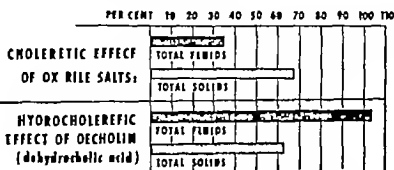
## PLYMOUTH

JANUARY 15. Brockton Hospital, Brockton.  
 FEBRUARY 19. Toll House, Whitman  
 MARCH 18. Goddard Hospital Brockton.  
 APRIL 15. State Farm, Bridgewater  
 MAY 20. Lakeville Sanatorium Lakeville

## WORCESTER

JANUARY 14. St. Vincent's Hospital.  
 FEBRUARY 11. Worcester State Hospital  
 MARCH 10. Memorial Hospital.  
 APRIL 14. Hahnemann Hospital.  
 MAY 12. Annual Meeting

## DECHOLIN HYDROCHOLERESIS Encourages Biliary Tract Drainage



Percentage Increase in Composition and Quantity of Bile Flow

Ivy A. C. et al: Am. J. Dig. Dis. 7:333 (Aug.) 1940.

## HYDROCHOLERESIS—

an increased production of thin liver bile—is a desirable approach to therapy of non-obstructive biliary tract disturbances.

## DECHOLIN—

by producing an increased flow of bile—washes stagnant, infected bile from the intra-hepatic and extrahepatic biliary passages, removing pus laden material and discouraging the ascent of infection

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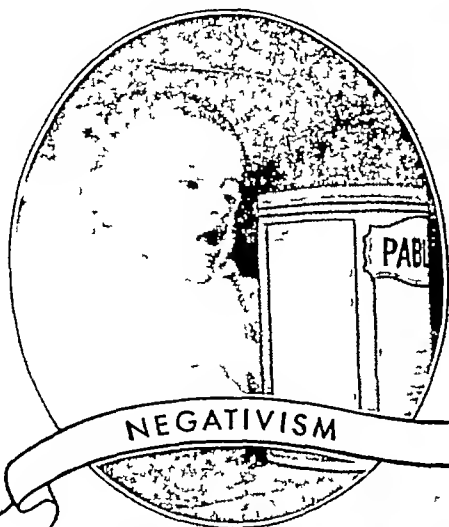
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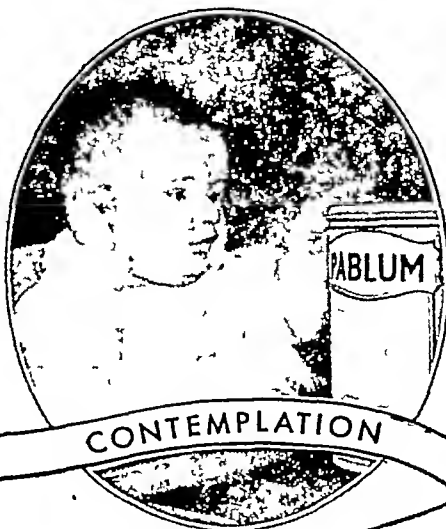
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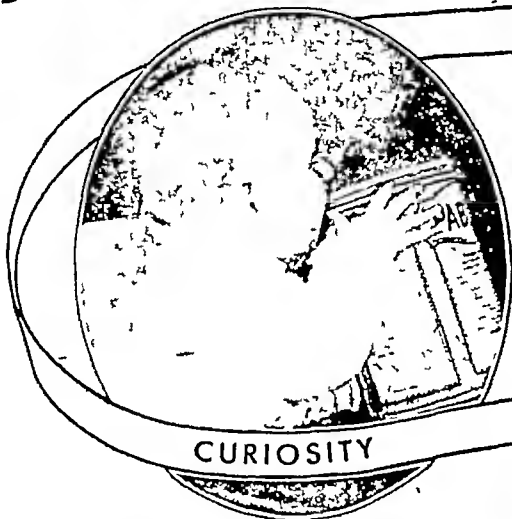
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 Boston, Mass.



NEGATIVISM



CONTEMPLATION



CURIOSITY



INTEREST



INVESTIGATION



ACCEPTANCE

# *A Young Lady's First Impressions*

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# The New England Journal of Medicine

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Volume 238

JANUARY 15, 1948

Number 3

## PRESENT-DAY STATUS OF POLIOMYELITIS\*

WILLIAM T. GREEN, MD†

BOSTON

**P**ERIODIC assessment of knowledge regarding infantile paralysis is highly desirable. I know of no other disease in which the public has such a great interest and, in turn, apprehension out of proportion to its incidence, morbidity, and mortality. Many sensational statements regarding new developments are reported in the lay press with very little corresponding information available in medical journals and without scientific confirmation. This makes it difficult for members of the medical profession not working in this particular field to keep informed regarding developments, real or alleged, affecting the disease. The public is much more likely to be aware of exaggerated, false claims than of actual scientific advances. Why should such sensational and unsubstantiated claims pervade the atmosphere in this disease?

The nature of poliomyelitis itself is the greatest factor. The disease is extremely variable in some cases it produces no recognizable paralysis, and in others it causes total paralysis, with all variants in between. The completeness of recovery depends to a considerable extent on the original degree of involvement, yet in the acute, preparalytic stage, it is impossible to estimate the amount of paralysis and disability that will occur. A considerable percentage of patients seen in this stage will recover completely if no specific treatment is given.

The original sampling of patients becomes a significant factor in determining the results obtained in any group of cases. If a report is based upon cases that are included in the series in the preparalytic stage, the results obtained will be statistically very good, since many of the patients will recover completely whatever the treatment they receive, whereas if the group is composed of patients who are admitted in the paralytic stage and of those who are referred when seriously involved, the apparent results will be much less favorable.

It is easy to produce a report indicating that a new treatment is excellent merely by establishing the criterion that the therapy is effective only if given in the preparalytic stage. Since many mild and nonparalytic cases will thereby be included, the recovery on a percentage basis will be excellent.

The problem of evaluating reports is further complicated by the fact that, owing to a chain of circumstances, many people have entered the field of therapy of infantile paralysis with little appreciation of the basic nature of the process and without previous experience.

In a disease of such characteristics, "new treatments" that are introduced are described as changing the prognosis radically. One of these new treatments that has been widely popularized was said to be based upon a new concept of the disease, in which paralysis was relegated to a minor role. This method was reported to be revolutionary in its results and was extensively publicized, this publicity marked the beginning of sensationalism in infantile paralysis, which still continues. Other treatments have been reported and carried to the public without scientific confirmation.

Furthermore, an organization, nationwide in scope, is concerned with raising funds to combat the disease. This keeps the subject before the public, and despite the desire of this organization to educate the public only in scientific facts, such a result is not always obtained. It should be the desire of the medical profession to keep the public informed of scientific achievements in medicine, but this educational program must involve substantiated scientific facts.

Knowledge regarding infantile paralysis is accumulating, not by revolution but by evolution. Research in this field has increased greatly in recent years, largely under the impetus given by the funds of the National Foundation for Infantile Paralysis. Important information has been added, and yet in its practical import the total contribution has been disappointing. This does not belittle the work that has been done or reflect on its necessary character.

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1947.

†Orthopedic surgeon-in-chief, Children's and Peter Bent Brigham hospitals; clinical professor of orthopedic surgery, Harvard Medical School; director, Massachusetts Infantile Paralysis Clinic, Children's Hospital.



In the field of epidemiology, for example, the usual method of spread of the disease still remains in doubt, although many factors regarding the natural history of the virus are better understood. The presence of the virus not only in the stools of patients and contacts but also in sewage and flies and the evidence of a carrier state tend toward a better understanding of the means by which the disease is communicated. The evidence is that the virus is quite widespread in times of epidemics and that relative immunity, at least to the neurotropic factors of the disease, plays a large part in the epidemiology. This may well be due to the fact that most people have had the disease in the subclinical form. Yet the usual method of transmission still remains unknown. Lack of this knowledge, incidentally, increases the apprehension of the public.

One feature of the epidemiology should be emphasized—the increased incidence of bulbar poliomyelitis in patients shortly after tonsillectomy. Since this is the form of the disease with the highest mortality, tonsillectomy performed during a poliomyelitis epidemic or when endemic cases are occurring is, under ordinary circumstances, undesirable.

It is impossible in a short time to discuss in any detail the recent contributions of research. Electromyography has been of assistance in interpreting the abnormal neuromuscular physiology in the disease. The neurotropic character of the virus and the diffuseness of the involvement of the nervous system have been confirmed and emphasized. However, we are still without a method of increasing either passive or active immunity to the virus. The real advance will come when infantile paralysis can be prevented, but for the present we are confronted with the necessity of treating the disease as effectively as we can to obtain the maximal functional result.

Before therapy is considered, certain clinical features of poliomyelitis should briefly be reviewed, and the pathologic process, so far as it is essential for this discussion, should be considered.

#### CLINICAL AND PATHOLOGIC CONSIDERATIONS

Infantile paralysis is characterized by an acute illness that, in its first phase, may be nonspecific but soon causes symptoms referable to the central nervous system, with increasing sensitivity, spasm and paralysis. Not infrequently, between the early nonspecific portion of the acute illness and the period when symptoms referable to the central nervous system occur, an afebrile stage of from one to five or even seven days may exist, giving a diphasic character to the acute illness. The acute febrile stage of the disease may be very short, but usually lasts from five to ten days, after which an increase in the degree of paralysis is rare. Death, if it occurs, is ordinarily due either to respiratory involvement or to bulbar paralysis.

Paralysis of recognizable degree may or may not be present, and the distribution is extremely variable. It may affect but few muscles, it may affect all. It tends to be regional in its distribution, although a patchy character is common. The effect on individual muscles varies from slight weakness to complete paralysis.

The particular combination of neuromuscular effects that the disease produces causes it to be deforming and disabling. The paralysis is the factor of chief importance, but in the early stage, the spasm contributes to the deformity and in turn to the disability. If one pictures a disease in which one group of muscles may be paralyzed, and the opposite group controlling the part are in painful spasm and shortened, it can be appreciated that deformity will result. This tendency is increased by the fact that carrying the part out of deformity is painful. To add to the difficulty, if parts are left for a period in a deformed position, a secondary myostatic contraction develops, and the deformed position becomes fixed. Furthermore, deformity, as well as sensitivity and muscle spasm, inhibits muscle function and, in turn, the return of muscle power.

Although the effect of the disease on the central nervous system is quite widespread, the main destructive action is on the anterior-horn cells, producing a flaccid paralysis. It should be emphasized that the action on the anterior-horn cells supplying a particular muscle may vary in all degrees up to their total destruction, and hence from temporary neuronal injury with rapid recovery of function to irrevocable paralysis. It must likewise be considered that weakness of a muscle, short of complete paralysis, is due to the involvement of a particular proportion of its neuromuscular units and that even in muscles severely involved one or more residual neuromuscular units usually remain. These, for purposes of therapy, are designated as "guiding contractile units."

If the involvement is severe, the recovery of the power of the muscles extends over a considerable period, but it usually may be said to be completed in sixteen months, with the greatest degree of recovery in the earlier part of this period. In the individual muscle, the prognosis for recovery cannot be anticipated in the early paralytic stage. The greater the degree of paralysis at the start, the less likely is complete recovery of the particular muscle, especially if the paralysis is equally extensive in the regional area.

The pathologic mechanism that produces the sensitivity and spasm remains unknown. Lovett years ago suggested that the involvement of the posterior ganglions might be the factor. The possibility that it is due to effects on the internuncial neurons or on neurons with an inhibiting or stimulating action on the anterior-horn cells has been proposed. It should be emphasized that the spasm

is not the most damaging effect of the disease, as proposed in the Kenny concept, but that it is a symptom that, with sensitivity, tends to be deforming in the early stages. Pain and muscle spasm inhibit muscle function during the acute stage, but the disability of consequence arises from the paralysis. Spasm becomes important in the end result only when paralysis exists.

### TREATMENT

Progress in the therapy of poliomyelitis has been one of gradual evolution based on physiologic principles as applied to the pathologic process. The flurry accompanying the Kenny method has receded. It has stimulated a re-evaluation of technics, and, in fact, in this way it has been most beneficial. Curare and prostigmine have not been demonstrated to be of particular value. Their use is based upon an idea that the spasm is of greater significance than present knowledge can substantiate.

Treatment depends upon the stages of the disease and the degree of involvement. It is best considered by subdividing the disease into three stages—a modification of Lovett's original classification. The first is the acute stage, which may be described as the period of the acute febrile illness, and which may, in turn, be subdivided into a preparalytic and a paralytic phase. The second is the convalescent stage or stage of recovery—the period during which muscles may recover their power—and may be said to end in sixteen months, this may be subdivided into the sensitive phase and the insensitive phase, the first, or sensitive phase, ending when the sensitivity and muscle spasm are no longer present. The third stage (the chronic or residual stage), which follows the convalescent stage, is the period after actual recovery of the muscles is to be expected, although the functional capacities of the patient may be greatly improved during this phase.

#### *Acute Stage*

In the acute stage, the treatment is mainly symptomatic. Bed rest is essential, and the patient's activities should be minimal under these conditions. He should not be allowed to wait upon himself. To carry the idea farther if, in epidemic periods, a patient has a minor illness of nonspecific character that might possibly be the first stage of the diphasic type of onset, his activities should be curtailed for a sufficient period after the temperature has returned to normal to establish the fact that the disease is not present. There is evidence, for example, that fatigue and overactivity during this period, such as swimming in cold water, increase the morbidity of the disease.

With the onset of symptoms referable to the central nervous system, such as sensitivity and spasm, heat in the form of intermittent hot packs may be applied to the sensitive areas as indicated, although prolonged hot packs, which are debilitating,

are contraindicated. When paralysis occurs, careful attention to the position of the parts, which must be supported and kept out of persistent harmful attitudes, should be given. Fixed positions for any considerable period should be avoided. Gentle handling of the patient is imperative, and sedation should be used as indicated. Sedatives should not be employed, however, as a substitute for good care.

During the stage of developing paralysis, the patient should be observed frequently for evidence of respiratory involvement or bulbar paralysis. If there are any signs of either type of involvement, constant nursing attention is essential, and the physician must be prepared to meet the emergency.

Bulbar involvement is indicated by such signs as difficulty in swallowing, changes in the voice and irregularity of respiration. Spinal respiratory paralysis is suggested by diminishing respiratory excursion, asymmetric or other abnormal yet rhythmic motions of the chest, use of the accessory muscles of respiration, shortness of breath and cyanosis.

These two types of involvement must be carefully differentiated, since the method of treatment of one is entirely different from that of the other, and to confuse them may result in a fatal outcome. In the bulbar type, the immediate indications are to keep the head dependent to allow for drainage, suction of the pharynx, parenteral feeding and manual aid to respiration if there are transient periods of difficulty. In the spinal respiratory type, the use of a respirator is indicated and may be lifesaving. Only rarely is a respirator indicated in the bulbar type of paralysis, as when the center actually fails completely or when the bulbar form is combined with the spinal respiratory type. Tracheotomy may occasionally be necessary but only on specific indication.

In patients with a fixed elevated chest, continuous local hot packs may be helpful. Feeding by gavage is contraindicated in the bulbar type of the disease if the patient cannot swallow, since vomiting may occur, with disastrous results. Continuous special care is essential in bulbar poliomyelitis since this type has a high rate of mortality that can thereby be greatly reduced. The problem in this type is emphasized by the knowledge that if a patient with bulbar poliomyelitis survives the acute stage, he usually recovers completely. I am particularly pleased to report that the death rate in infantile paralysis at the Children's Hospital, Boston, during the last three years has been slightly under 2 per cent.

#### *Convalescent Stage*

The return of the patient's temperature to normal marks no abrupt transition in treatment, but the therapy directed toward the neuromuscular abnormalities becomes more active. In the first phase of this stage, the patient is usually quite sensitive. All handling must be gentle, and motions of the involved parts should be assisted.

Hot packs are continued as indicated to alleviate the spasm, which of itself is deforming. Packs of the lay-on type are most frequently used. These may be applied several times a day and ordinarily are employed only on particular areas where the spasm is deforming and uncomfortable. It is well to add that hot packs have been used at the Children's Hospital during the sensitive stage of the disease for over twenty-five years.

In this stage, more effort is directed toward maintaining the desired anatomic position. Exercises involving gentle passive motions are performed several times daily to carry the position out of deformity and to develop an increasing range of motion. Correction at this stage should not be forced or painful. Parts are maintained in as good a position as possible and supported as necessary. Support to the feet in particular, whether with a portable foot support or a bedboard, is needed. The bedboard with the mattress pulled away from the foot of the bed (Kenny) allows the foot to be maintained at a right angle when the patient is prone. If it is difficult to control a deformity, bivalved plaster splints or wire splints are often indicated, particularly to support the feet. The splints are frequently used only part of the day and at night. This does not in any way deviate from the principle that parts should not be left in one position for long periods and in no way interferes with other factors of treatment.

An estimate of muscle function recording the degree of involvement should be made after the temperature has been normal for forty-eight hours, or shortly thereafter. This should be followed by an accurate "muscle examination" recording the functional power of the various muscles as soon as it can be accomplished painlessly and without disturbing the patient. This often needs to be done in piecemeal fashion. Such an examination is performed at regular intervals to record the progress of recovery. Active exercises are based on this examination.

Active guided exercises are added early on a graduated scale, discomfort and fatigue being avoided. These active exercises follow the principle that the weak muscles are required to carry out their function without allowing other muscles to substitute for their action. If a muscle cannot perform the action, the action is performed with a therapist assisting in the motion but with the patient making every effort to use the muscle. The position of the exercise varies according to the strength of the muscle and the function that can be elicited in the particular position.

These active exercises are based both on empiric observations and on physiologic principles. It is recalled that anterior-horn cells may be involved to any degree and that their function may be lost for a considerable period without death of the neuron and with consequent recovery of function.

Furthermore, if a muscle is left out of a particular pattern of motion for a period, it may recover its potentiality of function without returning to the pattern. During the convalescent stage when recovery is possible, it is quite important to maintain by exercises the action of the paralyzed muscle. If the weak muscle is not protected and stimulated to contract, and instead indiscriminate substitute motions are performed at all times, the weak muscle may drop out of the pattern completely. In this connection, it is well to remember that guiding contractile neuromuscular units exist for most muscles, even those severely affected. If all anterior-horn cells have been destroyed for a particular muscle, active exercises for this muscle are of no consequence. This, however, cannot be foretold during the earlier part, at least, of the convalescent stage.

Underwater therapy is highly valuable in the sensitive stage as well as in the later period of convalescence. The Hubbard tub is used early with the water at as high a temperature as is tolerated comfortably by the patient. This decreases the spasm and sensitivity and aids, with exercises in the water, in developing a range of motion and in correcting deformities. As the sensitivity decreases, exercises in a tub with water at a lower temperature and, in turn, in a pool, are of great assistance, particularly in patients who have considerable involvement.

*Insensitive phase.* After the insensitive phase of the convalescent stage is reached, actual stretching of the contracted parts is often necessary, and the active exercises are increased as tolerated. The first problem is to get the patient to use the afflicted muscle properly. Later, exercises are added that increase strength and produce hypertrophy. Part-time support for parts with deforming tendencies is often still needed.

Sitting and standing are ordinarily instituted in this stage also. This transition must be carefully supervised, and one must make sure that these activities are performed with as good a balance as possible without deformity being increased, and determine that the various muscles are used in as normal a functional pattern as possible. Crutches are often a desirable aid in walking at the start, depending upon the involvement of the arms. Walking braces are not ordinarily used during the convalescent stage until the maximal recovery of muscles has occurred, provided that the patient, when ready to walk, is able to walk without inducing further deformities. Walking of itself is an essential exercise if properly performed. Walking braces may be used during the latter part of the convalescent stage when it becomes apparent that they are necessary for effective locomotion. In the chronic stage, a brace should be used at least part time if the patient can walk more effectively with it than without it.

### *Chronic Stage*

In the chronic stage, the problem is to make the patient as effective as possible, despite the residual involvement. Particular cases may need regular stretching of certain parts. Muscles of borderline strength may need exercises designed to produce hypertrophy. Occasionally, support of one kind or another is needed for use at night.

Functional and gait training are most helpful in this period, particularly in patients who have had severe involvement or who have not been well supervised in their early course. Whereas, in the convalescent stage, muscle substitution is prevented, in this stage, if it is necessary, it is cultivated and supervised to produce the best function despite the paralysis. The adult may require little supervision in the chronic stage unless he has very extensive involvement, whereas the child with residual involvement should be supervised regularly during the growing period, since deformities may progress, owing to disturbances in growth.

It is also in the chronic stage that operative intervention may be indicated in such forms as tendon transplantation to supply a needed muscle function, fusion of parts by arthrodesis or corrections of deformities and improvement of function by other surgical means. Considerable progress has been made in the operative rehabilitation of patients in recent years.

\* \* \*

The treatment of infantile paralysis may be very simple in patients with mild involvement, and the outline of therapy presented above is interrupted as indicated. In a small percentage of cases it is a long, arduous task requiring highly skilled, patient, physical therapists and careful medical supervision by those experienced in the disease.

Ideally, it is believed that the patient with acute poliomyelitis should be supervised from the start by a team composed of a pediatrician or internist and an orthopedic surgeon, or at least someone experienced in the care of the musculoskeletal system in this disease. Attention must be given to the care of the musculoskeletal system from the start, thus preventing deformities and complications and simplifying the later treatment.

All patients, from the onset of the disease, are best cared for in a hospital. This would not necessarily be true if it were not for the possibility of a bulbar or respiratory paralysis. However, transportation of patients for long distances during the acute febrile stage should ordinarily be avoided.

Since an epidemic may occur at any time, one must be prepared to care for patients in the acute stage in local hospitals. After the febrile stage, if there is much involvement, treatment may be necessary in a special unit with an adequate staff of experienced physiotherapists, under proper supervision. It is well to recall that death, if it occurs, is most likely to happen during the acute stage, and the hospital caring for the acute disease must be prepared to give the best of supervision in this stage. In a large percentage of children the treatment after the sensitive period of the convalescent stage can be carried out at home if the mother is carefully instructed regarding the exercises and routine of care, and provided the child is supervised at regular intervals by the physician and physical therapist. The expense of care can thus be greatly decreased.

Knowledge of infantile paralysis is increasing, and therapy in the disease is improving, but not by any revolutionary discoveries.

## THE TREATMENT OF POLYCYTHEMIA VERA BY SPRAY IRRADIATION\*

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IN 1932 the treatment of polycythemia vera by spray irradiation was instituted at the Massachusetts General Hospital by the Department of Radiology at the suggestion of Dr Francis T Hunter. The results of treatment at the end of a ten-year period were presented by Robbins.<sup>1</sup> The purpose of this study is to report upon the present status of the original group of patients and also upon the results of treatment in 8 additional patients. This method of treating polycythemia vera has proved the most successful of any of the procedures that have been tried at this hospital, and it has seemed worth while, for the benefit of the clinician, to re-emphasize its value.

Irradiation of the bone marrow in cases of polycythemia vera was first suggested in 1907 by Stengel.<sup>2</sup> Lüdin,<sup>3</sup> in 1916, was the first to treat the disease successfully by irradiating the long bones of the skeleton. In 1932 Sgalitzer<sup>4</sup> reported good results from irradiation of the entire body. Similar reports followed from Hunter<sup>5</sup> and Sanderson<sup>6</sup> in 1936 and from Pierson and Smith<sup>7</sup> in 1940.

The investigations of Lawrence and his associates<sup>8, 9</sup> and others<sup>10, 11</sup> on the use of irradiated phosphorus suggest that in the future this may be the treatment of choice in polycythemia. The advantages of its administration are threefold: it causes less discomfort to the patient, its administration is easy, and it takes less time than irradiation by x-ray. On the other hand, a universal standard for measurement of radioactivity is lacking, and its long-range effects are still unknown. Radioactive isotopes, even though the "half-life" may seem safe, introduce a form of radioactivity whose long-term effects cannot yet be predicted. The same criticism may be applied to spray irradiation and may account for the reluctance of some physicians to make use of it. The experience at this hospital has been limited purposely to the use of the latter form of treatment because of its apparent success, and to keep this series of cases intact. The time may come, however, when radioactive isotopes will prove to be of greater value.

It is the policy of the hospital not to use any form of prolonged irradiation, whether for diagnosis, treatment or study, in persons who are not sick or who have a self-limited or benign disease. Polycythemia, however, whether neoplastic or not, in-

variably ends fatally and must be considered and treated as a malignant disease.

### METHOD OF TREATMENT

Spray irradiation is given with the intention of covering a field extending from the neck to the knees of the average person. This requires a long target-skin distance, which varies from 215 to 250 cm., and can usually be accomplished with a 20-by-20 cone on the machine. The area is centered at the level of the crest of the ilium, and anterior and posterior fields are treated on alternate days.

The following factors have been found satisfactory: kilovoltage of 200, 0.5 mm of copper and 1.0 mm of aluminum filtration, which gives a half-value layer of 0.92 mm of copper. The daily dose varies from 20 to 30 r, measured in air, and the total dose is approximately 300 to 500 r in any one series of treatments, divided between an anterior and a posterior field. The small daily dose usually prevents severe roentgen-ray sickness, and the repeated small assaults on the bone marrow may have a more prolonged effect than larger daily doses. Some of the first patients treated received larger daily doses and larger total doses, but the method outlined above has seemed to be safe and satisfactory. It produces fairly prolonged remissions without causing incapacitating radiation sickness, and with these doses there has been, with one possible exception, no definite injury to any of the patients.

The amount of treatment is determined by the total white-cell count. Such a count is taken at the beginning of treatment, at the end of a week, and at shorter intervals as the cells decrease, toward the end of treatment daily counts are taken. When the count falls below 5000 to 6000, treatment is stopped. No particular attention is paid during treatment to the red-cell count or to the hemoglobin level, since these determinations usually do not change significantly until a month or two after the treatment has been completed.

Tables 1 and 2 give the over-all results in 28 cases of polycythemia vera. To summarize the available data in a not too cumbersome form, certain laboratory findings, such as hematocrit determinations and oxygen-capacity studies, have been omitted. In the opinion of some investigators hematocrit determinations are considered indispensable in the treatment of patients with polycythemia vera. Experience in this hospital has shown, however, that the total clinical picture, together with white-cell and red-cell counts and perhaps photoelectric hemo-

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globin determinations, are sufficient and require considerably less time.

Twelve patients died, as compared to 16 who are alive. These results do not seem impressive until the causes of death are analyzed, many of the deaths were due to conditions other than polycythemia. Furthermore, this disease typically occurs in elderly persons, in whom life expectancy is short. In none of the group did leukemia, a leukemoid state or so-called "myeloid metaplasia" develop.

Table 3 presents details regarding the fatal cases. Two patients died of pulmonary disease apparently not related to polycythemia, 1 died of carcinoma of the breast two years after its discovery and eight years after irradiation for polycythemia had been started, and 1 died of uremia due to prostatic obstruction. It is not believed that these deaths were due either to the polycythemia or to its treatment.

Six deaths were caused by arterial thromboses (3 coronary, 2 cerebral and 1 cerebral, aortic and

It is difficult to assess the effect of polycythemia vera in producing vascular disease. Obviously, relatively few patients in this age group who develop

TABLE 1 Status of 28 Patients with Polycythemia Vera as of December 1946

STATUS OF PATIENT	No. OF CASES	INTERVAL SINCE FIRST TREATMENT		AVERAGE AGE AT TIME OF DEATH
		RANGE	AVERAGE	
Living	16	37	37	37
Dead	12	1 5-9 0	5 4	—
	12	1 5-11 0	5 6*	65 2

\*Omitting 2 patients who died during treatment.

vascular disease such as cerebral and coronary thrombosis have polycythemia. On the other hand, an untreated patient with polycythemia usually dies of vascular disease. Four of the patients who died

TABLE 2 Pertinent Data in Entire Series

HOSPITAL NO.	CASE NO.	SEX	AGE AT ADMISSION	TOTAL IR RADIATION	NUMBER OF COURSES	RED-CELL COUNT			INTERVAL SINCE FIRST TREATMENT	REMARKS*
						MAXIMUM	MINIMUM	FINAL		
						10 <sup>6</sup>	10 <sup>6</sup>	10 <sup>6</sup>	yr	
65650	1	M	52	1600	6	10.6	4.25	4.25	11 0	Death from lung sepsis
10179	2	F	49	1500	1	8.1	4.4	5.8	7 5	Sudden death (if coronary disease)
12970	3	F	38	600	1	7.5	5.7	6.05	7 5	Inoperable cancer of breast 2 yr. before death
312381	4	M	54	600	1	8.85	5.9	7.29	4 0	Patient failed to return for follow-up; death from cerebral thrombosis.
30101	5	M	62	1000	2	6.6	4.9	4.9	6 5	Death from stricture due to prostatic obstruction
8529	6	M	65	1000	2	9.9	7.3	7.2	0 0	Death 2 months after beginning of treatment (2nd series)
40036	7	F	50	1200	1	8.1	4.0	4.29	9 5	Very questionable exposure to benzene; patient well.
115021	8	M	62	1600	5	7.9	4.8	4.8	5 0	Death from cerebrovascular disease
142846	9	M	55	1675	2 5	6.9	4.6	4.69	8 0	Threatened gangrene subside
175527	10	F	70	700	2	8.9	4.2	4.76	4 5	Death from coronary thrombosis
163704	11	F	65	650	1	7.7	4.35	5.8	5 0	Death from cerebral and aortic thromboses
198686	12	F	61	900	2	7.1	2.02	4.16	7 0	Patient well
215758	13	M	47	5200	6	9.2	6.8	9.0	7 0	Unsatisfactory result; patient alive.
226399	14	M	64	500	1	7.7	3.7	5.9	7 0	Treatment refused 8/30/43; patient seems well.
253145	15	M	53	250	0.5	8.5	5.31	5.92	3 5	Incomplete treatment; death from (?) coronary thrombosis.
270452	16	F	57	1400	5	7.5	3.5	4.26	6 0	Dizziness regardless of red-cell count; patient alive.
287060	17	F	57	500	1	7.4	4.19	4.96	3 5	Patient well
306930	18	M	40	1210	3	10.5	2.3	4.42	5 5	Blood pressure of 220/130; patient who refuses hospitalization alive.
324094	19	F	76	180	0	10.5	—	—	—	Death 1 hr. after beginning of treatment (1 embolus)
126422	20	M	76	320	1	9.0	4.65	4.65	1 5	Death in nursing home cause unknown; probably polycythemia.
553441	21	M	15	700	2.5	9.8	5.5	6.54	5 5	Patient very young; no congenital heart abnormality; no benzene; still alive
558968	22	F	34	710	2	8.8	4.5	4.3	4 5	Amenorrhea, probably due to irradiation; patient alive.
596617	23	F	70	400	1	7.55	3.95	3.95	4 0	Venesection (2000 cc.) year before treatment; patient well.
2529	24	F	48	950	3	9.0	2.2	2.2	5 0	Increasing anemia; "marrow fibrosis" (?) benzene; patient alive.
348906	25	F	65	375	1	7.35	4.5	5.09	4 5	Patient well
364463	26	M	60	1650	4	9.27	5.6	4.7	4 5	Patient well
495184	27	M	45	400	1	8.92	5.06	5.06	1 5	Patient well — (?) exposure to benzene
43557	28	M	34	600	2	6.69	4.22	4.22	3 5	Patient well

\*Statements regarding survival apply to patients status as of December 1946.

subclavian) and can be attributed to the primary disease. One patient died of pulmonary embolism two weeks after the beginning of irradiation. The cause of death in another case is unknown, but it is attributed to polycythemia.

from such causes may actually have died because of insufficient treatment.

The status of the 16 living patients is presented in Table 4. Thirteen have no symptoms attributable to polycythemia. One patient has a dangerous

hypertension for which sympathectomy was advised but was refused, the blood picture is normal. Since the report published in 1944 another patient has developed an unexplained, refractory anemia, which must, for the present, be attributed to irradiation

Table 5 represents an attempt to estimate the amount of irradiation that will provide a maximum remission. The possibility of a cumulative effect of previous irradiation has not been excluded, and the data are hardly sufficient to provide a statistical

TABLE 3 *Data in Fatal Cases*

CASE No	FINAL RED CELL COUNT $\times 10^4$	FINAL WHITE-CELL COUNT	FINAL HEMOGLOBIN gm/100 cc	AGE AT DEATH yr	REMARKS
1	4.25	—	11.3	63	Cause of death undetermined, hemoptysis, bronchiectasis demonstrated by x-ray study, last blood smear that of sepsis, patient died 11 years after first treatment.
2	5.8	7,500	19.5	58	Sudden "coronary" death $7\frac{1}{2}$ years after first treatment.*
3	6.0	11,300	16.4	46	Six years after first irradiation patient found to have inoperable cancer of breast, death 2 years later.*
4	7.29	—	—	58	Patient died 4 years after treatment, cause of death, cerebral thrombosis.*
5	4.9	6,900	14.3	68	Patient died $6\frac{1}{2}$ years after first treatment cause of death, uremia due to prostatic obstruction.*
6	7.2	1,300	—	66	Patient died 6 weeks after completion of second course of therapy, headache, fever, hemoptysis, lung cavities demonstrated by x-ray study.*
8	4.8	—	—	71	Death of cerebrovascular disease in state hospital 5 years after first treatment.* No autopsy.
10	4.76	8,000	16.4	73	Patient died outside hospital $4\frac{1}{2}$ years after first treatment, cause of death, coronary thrombosis.
11	5.8	—	15.5	69	Death 5 years after first treatment, autopsy revealed thromboses of cerebral aortic, subclavian and carotid arteries, as well as gangrene of right arm.
15	5.9	—	18.4	56	Patient died $3\frac{1}{2}$ years after first treatment, myocardial infarction, insufficient treatment.*
19	10.5	22,000	23%†	76	Patient found dead in bed 2 weeks after beginning of treatment, cause of death, probably pulmonary embolus, no autopsy performed.
20	4.65	8,600	13.0	78	Patient died in nursing home $1\frac{1}{2}$ years after first treatment, cause of death unknown — probably polycythemia.

\*Patient died outside hospital, no autopsy performed.

†Sahli.

In this case benzene (benzol) may have been a causative factor of the disease, but in spite of this fact and the possibility that irradiation was responsible for the present anemia, irradiation would have been

basis from which to draw conclusions. In general, it appears that the larger the total x-ray dosage, the longer the remission. The size of the dose, however, is limited by an increasing tendency to leukopenia

TABLE 4 *Status of 16 Living Patients (as of December, 1946)*

CASE No	FINAL RED CELL COUNT $\times 10^4$	FINAL WHITE-CELL COUNT	FINAL HEMOGLOBIN gm/100 cc	INTERVAL SINCE FIRST TREATMENT yr	REMARKS
7	4.29	7,200	13.6	9.5	Headache and hypertension (blood pressure of 180/130) on admission, patient now well, blood pressure, 130/90.
9	4.69	10,500	13.6	8.0	Threatened recurrence of gangrene of toe (present on admission), subsiding; patient otherwise well.
12	4.16	—	14.2	7.0	Dyspnea, weakness and duodenal ulcer on admission; subtotal gastrectomy performed on 10/30/42, polycythemia recurred and treated; patient now well.
13	9.00	7,800	21.2	7.0	Patient uroco-operative, unsatisfactory ilioleal result.
14	5.93	—	18.1	7.0	Gangrene of right foot; amputation, patient now apparently well.
16	4.26	7,200	14.4	6.0	Dizziness regardless of red-cell count; patient otherwise well.
17	4.96	7,300	14.9	5.5	Dizziness and transient paralysis on admission; patient now well.
18	4.42	—	11.0	5.5	Headache and epistaxis on admission; blood pressure of 170/110, now headache and blood pressure of 220/130, house admission for (?) sympathectomy refused.
21	6.34	—	14.9	3.5	Youngest patient, (?) ruptured spleen on admission, "fainting spells."
22	4.30	—	13.2	4.5	Amenorrhea (probably due to radiation); patient otherwise well.
23	3.93	8,400	12.4	4.0	Throbbing headache on admission; now well.
24	2.20	2,200	7.0	5.0	Weakness and fatigue on admission; well until August 1946 when increasing anemia occurred. Marrow biopsy "myelofibrosis."† Benzene? anemia due to treatment.
25	5.09	—	14.3	4.5	Weight loss on admission; now well.
26	4.70	15,600	12.2	4.5	Memory difficulty on admission; Benzene exposure; now well.
27	5.06	8,400	17.5	1.5	Lack of left hand co-ordination on admission; now well.
28	4.22	5,900	17.8	3.5	Headaches and nosebleeds on admission; now well.

considered the treatment of choice. One patient, although still alive after seven years, has numerous symptoms and an increased red-cell count, and this case is considered a therapeutic failure.

The table suggests that a total dosage of between 400 and 500 r will produce good results.

The total white-cell count has proved the best criterion for determining the amount of irradiation

to be given. When the total count falls below 5000 treatment is discontinued. A count of 1800 or less has resulted from some of the larger doses, but there have been no symptoms and no fatalities from this cause. Especially during the early years of this type of treatment, some patients who received a relatively large dose experienced unusually long remissions of symptoms.

### DISCUSSION

The treatment of polycythemia vera by blood-letting is physiologically unsound for several reasons. Blood loss is known to be one of the greatest stimuli to bone-marrow activity and blood-cell production. Such a procedure relieves only one of the complicating factors—namely, increased blood volume; it does not affect platelet production, except by increasing it, and may have no effect in preventing vascular thrombosis. Most patients treated by this method are never quite well even when frequently

Phlebotomy may be indicated, however, for the immediate relief of acute symptoms or when disaster threatens.

Difficulties in the use of phenylhydrazine are well known and require little comment. One of the greatest is in regulating the dosage, since not only do different persons react very differently to the drug but also a single patient may react unpredictably to a constant dosage. Its advantage (or disadvantage?) over phlebotomy lies in the fact that materials necessary for the synthesis of hemoglobin are conserved, and "hypochromic polycythemia" does not develop so readily. The use of this drug has largely been given up.

Theoretically, the use of spray irradiation seems to be a sound approach to the problem since it aims to inhibit an overproductive bone marrow. The results in this series of patients tend to confirm this theory, many of the patients having normal blood pictures for long periods after treatment. A great

TABLE 5 *Effects of One Course of Spray Irradiation.*

X RAY DOSE	PATIENTS WITHOUT REMISSION	PATIENTS WITH REMISSION									
		0.5 gr	1 gr	1.5 gr	2 gr	3 gr	4 gr	5 gr	6 gr	8 gr	
1300	—	—	—	—	—	1	—	—	—	—	
800	1	—	—	—	—	—	1	—	1	—	
700	—	—	—	—	—	—	—	—	—	—	
600	—	—	1	—	—	1	—	2	—	—	
500	—	2	1	—	3	—	3	2	—	1	
400	—	1	1	4	4	4	1	—	—	—	
300	—	2	3	—	1	1	—	—	—	—	
200	—	1	1	—	—	—	—	—	—	—	

bled, they need so much medical attention that they consider themselves, and are considered to be, chronic invalids. Phlebotomy eventually results in a condition of plethoric anemia, or hypochromic polycythemia, which is incompatible with good health. Finally, many of these patients develop a condition, variously described as "lenkemia," "lenkemoid state" or "myeloid metaplasia," which ends fatally.

An example of this is the case of a private patient, not included in this series, who was referred for treatment, after repeated phlebotomies, because of gangrene of the fingers. The blood picture was that of extensive extramedullary hematopoiesis ("myeloid metaplasia") with a severe hypochromic polycythemia, a white-cell picture suggesting myelogenous leukemia and vastly increased platelets. The fingers healed after one course of spray irradiation, the blood picture returned to normal after two courses, but a fatal anemia developed after a third course, two years later, made necessary by a recurrence of impending gangrene in the fingers and by a greatly increased number of platelets. The patient refused to re-enter the hospital for transfusions and further study, and died at home.

advantage of this type of irradiation is that patients so treated are perfectly well, often for years, requiring little medical attention, except for an occasional checkup of the blood picture. Another advantage is the fact that it does not produce a plethoric hypochromia and does not end in "leukemia" or "myeloid metaplasia." Vascular thromboses appear to be checked, and life may be prolonged, perhaps for a considerable time. The data in this study, however, are obviously insufficient to justify any positive statement. (The deaths of 6 patients from vascular disease are discussed above.)

The disadvantages of spray irradiation, pointed out above, are the suffering caused by roentgen sickness, the time and effort consumed in completing a course of treatment, the possibility of producing a refractory anemia (one of the 28 patients treated has such an anemia, possibly or probably due to treatment), and the possibility of deleterious, long-range effects. Except for the patient with anemia and the possibility (rather farfetched) that carcinoma of the breast developed in another case as a result of roentgen irradiation, none of the group developed any such condition.



A statistical presentation of the results does not give a clear picture of the actual value of this form of treatment. The following of individual patients over a number of years, however, is very impressive, the results in a small group of private patients, not included in this report, are even more impressive. The following case is an example.

A 61-year-old woman with polycythemia was first seen in 1936. At that time she had numerous complaints, especially a severe type of peripheral neuritic pain. The red-cell count was in the vicinity of 11,000,000. In the past 11 years she has received four courses of spray irradiation, totaling 2100 r, and has remained entirely well. She is now 72 years old.\*

Although this is but a single case, no comparable result has been found in the reports of those advocating phlebotomy.

Further evidence of the value of spray irradiation therapy derives from the fact that it is resorted to when bloodletting has nearly resulted in death. Three such private patients have been seen at this hospital, 1 of whom died of anemia two years after spray treatment had been begun but who enjoyed better health during that period than he had for many years previously. A second patient, who had a very abnormal "leukemoid" blood picture with hypochromic polycythemia following many years of repeated phlebotomies, is at present well (two years after treatment), with a normal blood picture. The third patient is just completing his first course of treatment. It is not satisfactory to irradiate such patients with abnormal blood pictures due to long-continued bloodletting, they should rather be treated from the beginning by spray irradiation.

Another private patient not included in the group was discovered to have polycythemia vera as a cause for extensive venous, and probably, peripheral-artery thromboses. Bloodletting became impossible because of venous thromboses at the site of the venepuncture. The man was told that nothing more could be done for him. At that time, two years ago, a single course of spray irradiation was given. There has been no subsequent recurrence of thrombosis, and there has been a considerable improvement in the venous circulation.

It should be emphasized that spray irradiation may be a particularly dangerous form of therapy if employed injudiciously. Its use in patients whose increase in red-cell count and in hemoglobin is due to anoxia might prove fatal. Polycythemia vera, as the name implies, is a disease associated with a considerable increase in all the cells of the blood. This

\*Since this paper was submitted for publication, this patient has died of a condition clinically and pathologically indistinguishable from acute myelogenous leukemia.

is not true of secondary polycythemia or "erythrocytosis." Spray irradiation should never be used in cases of extramedullary hematopoiesis ("myeloid metaplasia") in which the marrow itself has been replaced by tumor or other tissue, for the results may well be fatal. Finally, the not too uncommon, benign condition of familial hypochromic polycythemia, largely confined to members of the Italian race, should never be treated by irradiation. In fact, these patients need no treatment of any kind.

For the reasons stated above, radioactive isotopes have not been used in the treatment of polycythemia in this hospital, and for the moment judgment on this type of therapy is reserved.

## SUMMARY

Twenty-eight cases of polycythemia vera treated by spray irradiation are reported.

Twelve patients are dead, 4 died of causes other than the polycythemia or its treatment.

Of the 16 living patients, 13 are free of symptoms attributable to polycythemia, 1 has hypertension, 1 is anemic, and 1 is still polycythemic and is considered a therapeutic failure.

One patient has a refractory anemia, possibly or probably attributable to roentgen-ray treatment.

No patient has developed leukemia, a "leukemoid state" or "myeloid metaplasia."

Phlebotomy is contraindicated in polycythemia vera except in the treatment of acute symptoms or impending disaster.

Spray irradiation is the treatment of choice.

The use of radioactive isotopes is discussed only briefly.

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## OVARIAN CONSERVATION DURING SURGERY

## With Reference to Bilateral Dermoids and Endometriosis

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CONSERVATION of portions of the ovary during surgery is not a difficult procedure, and yet it is not practiced commonly by general surgeons. Gynecologists are well acquainted with the fact that a very small amount of ovarian tissue will protect the patient's future well-being. Surgeons of lesser training and experience in this specialty are more likely to remove ovaries, probably because of a lack of knowledge of pathology. With increased information on this score, surgeons will remove fewer ovaries in toto and will make every effort to save as much ovarian tissue as possible.

This paper, therefore, is written to call attention to the benefits to be derived from resection, to supplement an article presented in 1939<sup>1</sup> and to make a plea for greater conservatism on the part of the surgeons dealing with ovarian surgery.

In the paper referred to, the case of a thirty-three-year-old patient was discussed.<sup>†</sup> The ovaries in this case were nearly the size of large oranges because of bilateral dermoid cysts. At operation, the right ovary was completely removed. The left was resected, a piece 1.5 cm. in diameter and as thin as a dime remained.

The pathological report, by Dr. M. F. Vidoli, was as follows:

The first specimen consisted of an ovarian cyst measuring 2.8 by 2 by 1.5 cm., and separately received with the same specimen a small, irregular, tooth-shaped section measuring 8 by 6 by 4 mm. Multiple sections showed the entire ovary to be replaced by a cystic cavity filled with greasy yellowish material and two small cysts, each measuring 6 mm. in diameter, filled with clear fluid.

The second specimen included an oval, smooth, yellowish-gray mass of doughy consistence, measuring 8 by 6 by 5 cm. Multiple sections demonstrated a large cystic cavity filled with yellow greasy material and a moderate amount of hair. Along one side, the wall became thicker, showing remnants of ovarian tissue and several smaller cysts filled with whitish gelatinous material.

The microscopical diagnosis was bilateral dermoid cysts of the ovaries.

Since the operation, which was performed on July 26, 1938, the periods have occurred regularly without undue event. Frequent pelvic examinations have disclosed no change in the residual ovarian tissue. This finding is entirely consistent with the opinion expressed by various pathologists that normal-appearing tissue is normal ovarian tissue, microscopically, in every respect. What is the rationale for removing both ovaries in such cases? Why

cause a complete menopause in a young woman? Why deprive a young woman of the possibilities of having children?

With these thoughts in mind, when a second patient with bilateral ovarian dermoid cysts presented herself, she was also treated conservatively. The subsequent history in this case<sup>‡</sup> provides such a direct answer to the questions asked above that the pertinent facts are related as follows:

During December 1936, F. W., a 28-year-old woman, reported for a premarital examination. She suspected no physical abnormalities since she had been in good health and since the menses occurred every 28 days and were of 3 days' duration. When informed of the presence of bilateral ovarian dermoid cysts and the possible consequences of the operation, she postponed her marriage and was operated upon on January 23, 1939.

The findings were strikingly similar to those in the case presented above. The right ovary was nearly the size of a large orange and was completely removed along with the tube that was attached to it. The left ovary was likewise enlarged. A small piece of normal-appearing ovary was located near the ovarian vessels. It was 'shaved off' and examined for bleeding. Since a slight ooze only occurred this piece was not further disturbed. As in the previous case it was hardly as large as a dime.

The pathological report by Dr. H. E. MacMahon was as follows:

One specimen consisting of an encapsulated structure, roughly round, measuring 7 by 5.5 by 5.5 cm. is pale yellowish pink. Along one side is a scarred projecting nodule, suggesting ovarian tissue. Section through this reveals a small follicular cyst (regressing corpus luteum). Section through the large mass shows a cavity filled with cornified epithelium. This can be peeled with some difficulty from the wall leaving a smooth glistening surface. At one point there is a small bony, hard spicule. In another, there is a small cyst filled with gelatinous mucus-like material. The gross diagnosis is epidermoid cyst.

The second specimen includes a similar cyst, which is roughly round, rather soft and buttery. There is one small, bare area. The wall measures 0.1 to 0.2 cm. in thickness. The cyst is filled with buttery, white material that can be easily removed leaving a clean surface with the exception of one point where there is a projecting nodule from which a large tuft of black hair protrudes.

The microscopical diagnosis of the first specimen is epidermoid cyst of the ovary with a small follicular cyst and that of the second, dermoid cyst showing skin and skin appendages, cartilage, smooth muscle and abundance of myelinated and nonmyelinated nerve fibers; ganglion cells of the sympathetic system. There is no evidence of malignant changes.

Two weeks after the operation, a regular period occurred. After this reassuring episode, the patient completed her plans for marriage. Nine months after the operation she skipped two periods and then flowed profusely. There was some question whether she had had a miscarriage. Subsequently she was delivered of healthy well-formed babies on October 24, 1940, December 22, 1944 and October 13, 1946.

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†Cambridge Hospital Case 5-38-518 (July 6, 1938).

‡Cambridge Hospital Case 5-39-57 (January 23, 1939).

These cases demonstrate that adherence to the advice in the older textbooks "to remove both ovaries in cases of bilateral dermoid cysts" not only is unwise but also may be calamitous

As a matter of fact, papers have appeared only recently, urging conservative ovarian surgery in such cases. An extensive search of the literature disclosed few such articles. Usually, reference to the use of conservatism is hardly more than perfunctory. So little is said that unless one is particularly interested, it is taken for granted that radical surgery is the technic to be employed in all cases of bilateral ovarian dermoid cysts.

Geist<sup>2</sup> presents photographs of a dermoid cyst resected from an ovary. Study of this illustration is interesting because it discloses a very wide resection. It seems that in his case much more normal tissue was found and retained than in either of the 2 cases described above. This photograph again emphasizes the fact that one must have the will to preserve normal tissue.

Martzloff<sup>3</sup> describes a case of a thirty-nine-year-old woman from whom, at operation, he removed the left tube and ovary, resecting the right ovary. In describing this case, he states that the right ovary was about twice the normal size. It contained a yellowish cyst, through the wall of which some hair could be seen. This cyst was resected, what would correspond to about a third of a normal ovary being left in situ. The pathological report stated that section revealed a cystic structure filled with sebaceous material in which there was some hair. The author finally commented that when last heard of the patient "had been menstruating normally at twenty-six-day intervals."

This case affords a good illustration of the possibility of conserving the ovarian function when some normal tissue is present, the danger and inconvenience of a premature operative menopause being thereby avoided.

It is interesting to note how casually Martzloff comments on avoidance of a premature operative menopause. I believe that his statement bears greater emphasis because this patient was already near the menopause (age thirty-nine) and yet the author thought in terms of preventing such an occurrence earlier than it would have taken place naturally. This is the type of reasoning that more surgeons should follow. I can say, regretfully, that I have heard many surgeons remark at operation that the patient was near the menopause, anyway, and that the ovaries would be removed "to prevent trouble later on." Such loose thinking, in my opinion, is as illogical as extirpating an eyeball from the surface of which a cinder has been removed "to prevent trouble later on."

Martzloff concludes "Out of a total of some 200 patients who have had dermoid cysts in one or both ovaries (confirmed by examination of micro-sections) we have had only one other case (two altogether),

of carcinoma developing in an ovarian dermoid cyst" (His reference is to cases at the Johns Hopkins Hospital.) This remark can well be appreciated for the important reason that it disproves so effectively what is written in textbooks as dogma that most ovarian dermoid cysts become malignant, which they obviously do not.

Furthermore, Marshall,<sup>4</sup> in a brief report, presented evidence on 415 cases of dermoid cyst, examined at the Mayo Clinic. Among other facts, he disclosed that in this series 19 per cent were malignant. Bell<sup>5</sup> believes that few surgeons give any consideration to the surgical treatment of innocent neoplasms other than the complete removal of the organ and states that, as a rule, some healthy portion of ovary can be preserved with its normal connections, for nearly every neoplasm tends to grow away from the hilus and the preservation of this, with adjacent ovarian tissue, leaves well nourished and functional tissue. Mathews<sup>6</sup> also emphasizes the wisdom of conserving ovarian tissue and points out that the line of cleavage between the cyst and ovarian tissue can easily be followed. Miller,<sup>7</sup> in a general discussion of 90 cases of ovarian dermoid cyst, concludes that conservation of ovarian tissue by enucleation of the dermoid cyst is an easy and valuable procedure.

If the advice given in the statements presented above is followed, it will quickly be discovered that this type of surgery is not too difficult. It is important, however, to operate with great care, so as not to disturb the blood supply of the tissues to be retained. It must be kept in mind that no matter how small the piece of remaining ovarian tissue is, it is well worth conserving.

The following authors are quoted because their papers likewise express the belief that it is not difficult to remove the cystic portions.

Dockerty,<sup>8</sup> of the Mayo Clinic, reviewing four hundred articles in the literature on the subject of ovarian neoplasms in general, states "When such small dermoids are encountered they should be shelled out without rupture and the resulting raw surface apposed with a minimum of fine suture material. Pregnancy has occasionally ensued after such conservation of the ovarian tissue."

I believe that it is possible to extend these remarks by the statement that conservative surgery can also be practiced in cases with large dermoid cysts. The cysts in the cases described above were each nearly the size of an orange.

Meigs<sup>9</sup> writes that dermoid cysts may be treated by excision with the ovary or excision from the ovary. He also concludes his discussion of ovarian tumors by saying "The treatment of certain ovarian lesions is definite and may be conservative. . . ."

The following cases are included in this paper because they likewise help prove the value of conservative ovarian surgery. These were cases of endometriosis, reasonably well developed, in patients

who before operation had been considered incapable of bearing children

J P \* a 22 year-old woman who had been married 13½ years, had been well up to 6 months prior to operation. During that time increasingly more painful menstrual periods had developed. On August 30, 1944, she was operated upon by me at the Cambridge Hospital. Owing to a chocolate cyst, the left ovary was nearly the size of a peach. The tube was intimately adherent to it. The uterus was in retroversion. The right tube appeared normal. The right ovary contained simple cysts. There were numerous endometrial implants over the surface of the bladder. A left salpingo-oophorectomy, incision of the cysts of the right ovary excision of the endometriomas and uterine suspension were performed.

Pathological examination by Dr MacMahon disclosed an endometrial cyst of the ovary with endometriosis of the tube and of the adjacent serosal surface. The ectopic endometrial tissue was "in secretory phase" as was the endometrium.

In November, 1945, the patient's husband returned from military service. She became pregnant during January 1946, and was delivered (because of disproportion) by low cervical cesarean section on November 2, 1946, of a healthy female baby weighing 7 pounds, 13 ounces. At this operation, the remaining right ovary was examined. It was normal in appearance.

This case also demonstrates the value of conservative ovarian surgery. It may seem that this point is being labored. If reiteration drives home a thought, it is well for the occasional operator, especially, to appreciate the value of conservatism. My belief is that this advice cannot be repeated too often and that the lives of many women, as well as their marital relations, can be saved from being wrecked by exceedingly small pieces of ovarian tissue. Greater caution must be exercised by the surgeon in his decision to remove one ovary even if the other is normal. In many cases, resection of a pathologic ovary leaves enough functioning tissue to give the patient two functioning ovaries against the possible future ravages of time.

The following case falls into a similar category.

G M a 26-year-old woman had been married 5 years and had been unsuccessful in becoming pregnant. An extensive abdominal operation was performed by another surgeon in 1942. The patient was informed that part of an ovary had been removed during this operation. Subsequently, she continued to have severe pain during the menstrual periods. Examination in January, 1944 disclosed enlargement of the left ovary to nearly four or five times the normal size. On January 19, 1945, I performed lysis of intra abdominal adhesions, a left salpingo-oophorectomy and partial resection and repair of the right ovary.

The left ovary was enlarged about four times the normal size, owing to "chocolate" contents. A presacral neurectomy and excision of multiple endometriomas were done. The right ovary contained a chocolate cyst, which was resected.

The pathological report disclosed "chronic perisalpingitis and peri-oophoritis, and endometrial cysts of the ovary."

This patient was urged to try for pregnancy soon after her discharge from the hospital and on April 4th, she had her last regular menstrual period. On January 18, 1946, after a test of labor this patient was delivered (x ray measurements — diagnosis of disproportion), by low cervical cesarean section, of a normal, male baby weighing 6 pounds 6 ounces. At operation the remaining right ovary was examined. It appeared normal.

## DISCUSSION

In these cases conservative ovarian surgery was practiced. The older textbooks invariably advise the complete removal of ovaries in such cases. If this advice had been followed in the cases described above, the patients would have lost completely the opportunity of becoming pregnant, would have suffered sudden surgical menopause and would also, as a result of these changes, have had difficulty in their domestic welfare.

Reference has been made to "older textbooks." As a matter of fact, even recent articles in the medical literature seldom allude to the use of conservative surgery. This paper, therefore, is written as a plea that the surgeon consider carefully his decision to remove ovaries, that he remember the dire consequences from the removal of both ovaries in young women, and that he preserve as much ovarian tissue as possible.

## SUMMARY

Four cases in which both ovaries were not removed, even though the tissues were pathologic, are cited.

Two cases of bilateral ovarian dermoid cysts are described. In both, dime-sized portions of tissue were preserved. One patient, who married later, was subsequently delivered of 3 normal children.

Two cases of endometriosis are reported, both with endometrial implants and involvement of both ovaries. In each, one ovary was removed. The remaining ovary was partially resected. Both patients were subsequently delivered of normal healthy babies and had regular painless periods after these deliveries.

In the treatment of a large number of women over a period of seventeen years, conservative surgery has been practiced in numerous cases, and the final results have been most gratifying.

The 4 cases described were chosen as the most suitable to drive home the point that conservative ovarian surgery is possible and ultimately pays large dividends to the patient.

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## CLINICAL NOTE

## THORACIC TENDERNESS IN PULMONARY INFARCTION

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**D**URING the last decade, steadily increasing attention has been paid to the early diagnosis, in both medical and surgical cases, of phlebothrombosis and thrombophlebitis. Earlier diagnosis and prompt treatment with the anticoagulants, or by venous ligation, have appreciably reduced the number of unfortunate cases in which the patient, making an uneventful convalescence, suddenly succumbs to a pulmonary embolism. However, in spite of routine daily examinations of the legs and scanning of the chart, the first evidence of such a process is all too often observed too late.

Boyd<sup>1</sup> divides pulmonary emboli into three classes: large emboli occluding a main artery and causing death with respiratory distress, medium-sized emboli producing physical signs of an infarct; and small emboli causing symptoms but not physical signs of infarction. It is the purpose of this communication to describe a physical sign that occurs in the small emboli in the third classification.

It is important to make the diagnosis of pulmonary infarction and institute treatment immediately after the episode has occurred, since there is no assurance that a second, and perhaps fatal, embolus will not occur at any time. Yet x-ray study cannot be expected to confirm the diagnosis for nearly twenty-four hours, and physical signs in the lungs are totally absent if the embolus is small and may be equivocal if it is present.

An early and striking finding in 4 well established cases of pulmonary infarction occurring postoperatively, and in 1 equivocal case occurring in an orthopedic patient, has been marked tenderness of the chest wall, approximately over the site of infarction. This tenderness in all cases was severe enough to cause the patient to cry out and flinch if moderate pressure were applied. It was present in 1 case as early as six hours after the initial onset of pleuritic pain and disappeared gradually in from forty-eight to seventy-two hours. The area of tenderness varied in diameter from 2.5 to 20 cm, presumably depending on the extent of the underlying pleuritis, and in each case a sharply demarcated point of maximum tenderness could be demonstrated in one of the intercostal spaces.

Brief abstracts of the pertinent data in 5 cases follow.

**CASE 1.** A 39-year-old housewife developed severe pleuritic pain in the right anterior portion of the chest 11 days after

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choledochostomy. The temperature rose to 100°F. Examination revealed exquisite tenderness in the right anterior portion of the chest with point tenderness in the sixth interspace in the anterior axillary line. The lungs were clear, and x-ray examination of the chest was negative. There was tenderness in the calves of both legs with a positive Homans sign on the left. A bilateral femoral ligation was performed.

**CASE 2.** A 20-year-old girl developed acute deep thrombophlebitis of the left leg on the 8th day after ileostomy for ulcerative colitis. This was treated by repeated paravertebral blocks, caudal blocks and heparin-dicoumarol anticoagulant therapy. On the 9th postoperative day, a mild pleuritic pain developed in the right anterior portion of the chest without other symptoms. Physical examination showed point tenderness in the sixth interspace in the anterior axillary line, but the lungs were clear and x-ray study of the chest was negative. On the following day a friction rub was audible in the involved area.

**CASE 3.** Eight days after a cholecystectomy, a 53-year-old housewife developed pleuritic pain in the right posterior portion of the chest that was so mild that she did not mention it for 24 hours. There were no other symptoms. The temperature was 99°F, and the respirations 28. There was definite tenderness over the right lateral and posterior portions of the chest with point tenderness. There were suppressed breath sounds and moist rales in this area. X-ray study of the chest was interpreted as showing atelectasis. There was questionable tenderness over the left femoral vein. Anticoagulant therapy was instituted.

**CASE 4.** A 25-year-old man, scheduled for exploratory laparotomy, had operation delayed for 10 days pending evaluation of deep tenderness noted first in the right calf and later in the left calf. There was no elevation of vital signs, and Homans sign was negative. However, on the 1st postoperative day there was gross hemoptysis. On the 2nd postoperative day the patient noted severe pleuritic pain in the right anterior portion of the chest. There was extreme tenderness in this area. The temperature rose to 102°F, the pulse to 110, and the respirations to over 30. X-ray examination showed consolidation of the right lower lobe. Anticoagulant therapy was instituted.

**CASE 5.** A 73-year-old woman had been in bed 3½ months, after an open reduction and nailing of a fractured hip, when she developed a sharp pleuritic pain in the left anterior portion of the chest, which lasted for 3 days. There was point tenderness in the fifth interspace in the anterior axillary line, but physical examination was otherwise negative, with no signs of phlebothrombosis. X-ray study of the chest 3 days later was negative. No therapy was instituted, and no further episode occurred.

It is significant that in none of the cases did there appear the combination of symptoms and signs that are generally considered typical of pulmonary infarction — that is, cough, hemoptysis, pleuritic pain, fever, increased respiratory rate, distant bronchial breath sounds, moist rales and x-ray evidence of infarction. Two cases showed pleuritic pain and thoracic tenderness alone, whereas another had a transient friction rub in addition that could easily have been missed. Only 2 cases revealed changes in the lung by physical and x-ray examination.

It is also significant that in 1 case the diagnosis of pulmonary infarct was not considered during the hospital stay, and that in another, a delay of several hours ensued before the true nature of the episode was appreciated and ligation performed. In a third case the symptoms were so insignificant that the patient did not mention them until twenty-four hours had elapsed.

The significance of this sign (thoracic tenderness), which is certainly neither new nor unknown, is apparently not widely appreciated. A survey of the standard textbooks of medicine and physical diagnosis, as well as various systems of medicine and texts on differential diagnosis, failed to elicit any reference to the sign. A review of the literature for the last ten years, however, resulted in the finding of one paper on the subject. McMillan,<sup>2</sup> in 1942, described extreme tenderness on light fist percussion over the affected area in cases of pulmonary infarction and reported 14 cases. He considered this sign

of great value in the differentiation of pulmonary infarction and pneumonia.

It is suggested that the presence of chest tenderness in connection with a pleuritic type of pain in the absence of trauma be considered suggestive of pulmonary infarction, even in the absence of supporting symptoms, signs or x-ray changes and that treatment be undertaken on that basis.

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## MEDICAL PROGRESS

### SYPHILIS

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AT THE time of this writing it is approximately four years since the publication of the first report on the use of penicillin in the treatment of syphilis.<sup>1</sup> The remarkable efficacy of this drug in combating man's most crippling venereal disease is attested by the fact that in so short a time it has become accepted as standard therapy for syphilis. A vast effort has been expended in widespread and well organized research projects, both experimental and clinical. From ten to twenty years are required to evaluate properly the therapeutic results of any approach to syphilis in all respects except immediate effects on fresh infections. The response of early syphilis to penicillin has been so dramatic, however, that the acceptance of this drug is now granted. Its long-term results will have to await further and prolonged observation periods. Despite this remarkable new weapon and the extraordinary success achieved by the military forces during the war, the trend of venereal-disease incidence is again on the rise.

#### PUBLIC HEALTH

The advent of penicillin has resulted in an increase of the treatment of syphilis by physicians engaged in diverse types of practice. This antibiotic has simplified the treatment of syphilis to the point where it can be administered by most practicing physicians with a modicum of danger. Anyone except those in more remote specialties can treat the disease, provided their plan of therapy is adequate. Two main pitfalls enter into the problem at this point. With such increased ease of therapy, a natural hazard is the possibility of treatment

without accurate diagnosis. Cases of this sort have come to the attention of most syphilologists in which physicians with undoubted skill in their own fields of work have too readily assumed the diagnosis of syphilis and instituted treatment. There are few diseases with more sociologic import than syphilis, and one should exert extreme care in making the diagnosis, entirely aside from the medical implications. Syphilologists, more than other physicians, are extremely loath to make a diagnosis of syphilis without unequivocal evidence, this applies particularly to the primary and secondary stages of the disease. The second and possibly even greater hazard in the treatment of syphilis by physicians in general practice is the likelihood of employing insufficient dosage of penicillin. There are many facets to this problem that have not been worked out satisfactorily, and programs of therapy are still constantly being changed. Penicillin causes so comparatively few reactions that overdosage is far less hazardous than with any other treatment for syphilis. Consequently, it is better to err on the side of giving more penicillin than is thought necessary, rather than using insufficient quantities. This will obviate the likelihood of infectious relapse that might easily go unrecognized until many more persons had been infected. It should not only increase the percentage of immediate "cures" but also go far toward preventing the late serious crippling sequelae of syphilis. The economic burden already entailed by syphilitic inmates of mental institutions is far too great. During the decade 1935-1944, inclusive, first admissions to mental hospitals in the United States due to syphilis, of all varieties comprised a rather high percentage, exclusive of the

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### *Statistical Trend*

The remarkable accomplishment of the military forces during the war in keeping the incidence of venereal disease lower than any previous wartime rate in history is well known. A survey of venereal diseases among the civilian population during the same period shows a trend that is not so encouraging.<sup>3</sup> The cases of syphilis diagnosed in the states and territories during the years 1941-1947, inclusive, and excluding all military sources, reveal a different state of affairs. During the first two years of the war, cases of syphilis reported for the first time among civilians increased steadily to a maximum of 576,000 in 1943. For the next two years, there was a significant drop, a low of 368,000 cases being reached in 1945. An increase of about 0.5 per cent, which was not significant, took place in 1946, and one of somewhat over 5 per cent was reported for the first half of 1947, which is a strong indication for the need of more urgent control measures. The majority of this elevation in rate took place in primary and secondary cases, pointing to the existence of reservoirs of readily available fresh disease. When further broken down, the statistics show a steady decrease in the number of late, late latent and congenital cases of syphilis during the same period of six years. These figures reflect the effectiveness of control measures that were carried out by both the armed forces and the United States Public Health Service. This downward trend in late crippling disease and congenital infections will not be maintained if the incidence of fresh infections continues to rise.

A purely military survey indicates a similar but more pronounced trend.<sup>4</sup> The report shows that a distinct increase in venereal disease became evident in the navy soon after VJ Day. This was reflected in all naval districts and made venereal disease the outstanding factor in morbidity at that time. The most marked increase was apparent in noncontinental areas and ships, in continental naval districts the increase was equally consistent, though slower. Naval personnel in the West Pacific area sustained the greatest increase of venereal disease, the rise in rate multiplying more than elevenfold in one year. Although military personnel has been drastically reduced since the war, there has been no relaxation in the attempt to control venereal disease in that quarter. A working agreement has been reached between the Army, Navy, Coast Guard, Federal Security Agency and American Social Hygiene Association, establishing peacetime relations in venereal-disease control.<sup>5</sup> In addition to the maintenance of military measures, this includes procedures by all public-health departments directed toward case finding, diagnosis, treatment and repression of sources of infection among the civilian population. The armed forces will continue to declare "out-of-bounds" establishments

that serve as places of pickup. The United States Public Health Service will continue to assist and co-operate with public institutions and scientists in the conduct of research and experiments relating to diagnosis, treatment and control of venereal disease.

There has been an impression that in recent years syphilitic infections among the teen-age groups have constituted an increasing proportion of the problem of venereal-disease control. It has also been thought that the vast numbers of men in military service who were concentrated in encampments had a pronounced influence on venereal-disease rates. An analysis of statistical data concerning patients admitted to public clinics for early syphilis from 1941 through 1944 contradicts these impressions.<sup>6</sup> The analysis was limited to females and indicated that a shift into the teen ages has not been nationwide and that a tendency toward an earlier age of infection among white females was most pronounced in the presence of an increasing civilian population, particularly in areas of war-boom industrial concentration. Increasing military populations seemed to have little or no tendency to be associated with an increased proportion of teen-age infection among white females, presumably because of active control measures within the armed forces.

### *Control Measures*

There are many communications giving evidence of the awareness of public-health authorities of the increased menace of syphilis. Information regarding sources of infection has always been difficult to obtain. Self-interview forms have been devised to elicit information from reticent patients.<sup>7</sup> These forms include pertinent advice regarding the danger and infectiousness of venereal disease and thereafter request information regarding sex partners, but do not require the patient to sign his name. The information is thus confidential, and co-operation is sometimes more readily obtained. Studies of epidemiologic activity on syphilis contacts reveal that approach by telegram, by visits to the patient and by letter all have their value in persuading suspects to report for examination.<sup>8-10</sup> Telegrams sometimes have a surprisingly effective result and may be even more efficient than a direct personal visit. Registered mail is obviously more impressive than ordinary letters. Personal visits take time and are expensive and comparatively slow, both in finding contacts and in returning patients to treatment. Compulsion is an effective but also an expensive method of case holding and cannot be used until a considerable time has elapsed since the patient's last treatment. Telegrams and registered letters are to a large extent effective in solving these problems. Compulsory attendance for an examination, for treatment or for those who have permitted therapy to lapse should be avoided if



possible Co-operation is not obtained by compulsion, and compulsion should be used only as a last resort.

Postgraduate instruction in venereal-disease management is available in almost every medical center of the country. Postgraduate refresher courses are being organized throughout practically every state. The practicing physician and public-health officer should be brought up to date regarding new methods of treatment and recent refinements in the diagnosis of venereal disease. Diagnostic and consultation services are available to physicians in nearly every community through clinics, medical schools and public-health agencies. Training or refresher instruction can be obtained either on an individual or a group basis, and if practicing physicians avail themselves of these opportunities many unfortunate errors can be avoided, simultaneously, an increased efficacy of venereal-disease control can be attained.

The importance of nurses in venereal-disease control is being more properly emphasized. The value of a nurse as a case finder cannot be overestimated.<sup>11</sup> An alert nurse in clinic, school, industry or on visiting-nurse duty can find many opportunities in her daily routine to serve as a case finder. Patients will sometimes more readily confide in a nurse than a physician and with proper interviewing may reveal contacts that would otherwise be undiscovered. The industrial nurse's responsibilities in venereal-disease control have increased since the end of the war.<sup>12</sup> The interests of management and labor in a good educational program are being stimulated. The industrial nurse fits neatly into this program both from the educational standpoint and in assisting case-finding measures. She has many opportunities for personal counseling with employees in family health problems and can include many phases of venereal-disease control. In a large clinic the nurses are responsible to a great extent for the atmosphere of the clinic and are an important factor in obtaining the co-operation of the patients.<sup>13</sup> The nurse may serve as a liaison between the doctor and the patient and between the patient and his family when trouble arises. She can often explain to the patient the physician's recommendation for the need for treatment of himself as well as contacts. Nurses may have more tact and ingenuity than physicians in many instances. Their responsibility in the education of the patient is of great importance. This is especially true of the public-health nurse in rapid-treatment centers, where the nurse is of inestimable value.<sup>14</sup>

#### *Morbidity and Mortality*

Among 3970 autopsies performed at the Yale University School of Medicine between 1917 and 1941, 380 showed evidence of syphilitic infection.<sup>15</sup> Of these patients 198 (52.1 per cent) had never received treatment. Anatomic lesions of syphilis were found in 77 (38.9 per cent) of these untreated

patients, but in only 46 (23.2 per cent) was death considered to have been due primarily to syphilis. One hundred and twenty-one patients revealed an absence of anatomic lesions of syphilis, and in 35 cases the serologic tests for syphilis were negative during the last hospital stay. The 77 untreated patients with post-mortem changes revealed 88 cardiovascular lesions, 8 lesions of the central nervous system and 10 other types of lesions. These results closely agree with the observations of Bruusgaard,<sup>16</sup> who was the first to report an authoritative series of untreated patients examined pathologically years later. The current report is an important study, and it should be read in the original by all syphilologists.

A survey by the Bureau of the Census of vital-statistics rates in the United States reveals a steady decline in the death rate from syphilis from 1938 to date.<sup>17</sup> There has surely been no de-emphasis of syphilis as a cause of death nor any decrease in the ability of doctors to recognize it during this time. Therefore, it is believed that this decline is a real one that can be attributed to the venereal-disease-control program. Evidently the treatment schedules advocated in the last few decades have been to good effect. As might be expected, the decrease in infant mortality due to syphilis has been even more pronounced. A survey of the most recent communications on the mortality of syphilis has given rise to formulation of a policy regarding the eligibility of syphilitic persons for life insurance.<sup>18</sup> This study and its recommendations regarding eligibility for insurance have been carried out by eminent syphilologists rather than the usual actuarial approach of insurance companies. It is of primary value and interest to the insurance actuaries but contains information valuable to anyone dealing with syphilis. The various types of the disease are classified regarding insurability, adequacy of treatment and probationary periods required after treatment before insurance should be granted.

#### EXPERIMENTAL STUDIES

##### *Penicillin in Oils*

Although penicillin in peanut oil and beeswax has been under study for some time, a recent report indicates that it may not be the best combination for delaying absorption of the antibiotic.<sup>19</sup> Injections of calcium penicillin of high potency suspended in hydrogenated cottonseed oil were found to maintain a penicillin level of 0.1 unit per cubic centimeter of blood for at least six hours in 80 per cent of cases, whereas in the beeswax-peanut-oil mixture it maintained that level in only 66 per cent. Hydrogenated oil delayed the absorption of penicillin more than the plain oils in all the various diluents tested. Undoubtedly, a good deal more work must be done along these lines before the best preparation is ultimately identified.



In experimental syphilis in rabbits, the effect of penicillin in peanut oil and beeswax has been compared with penicillin administered in isotonic solution of sodium chloride<sup>20</sup> The oil-wax suspension was definitely more therapeutically effective in the treatment of syphilitic orchitis of rabbits. When a single minimum curative dose of penicillin was employed, the oil-wax suspension was approximately ten times more efficient. When a single daily intramuscular injection was used for eight days in succession, the oil-wax suspension of penicillin required a minimal curative dose approximately one fifth as large as the saline solution. This work has been confirmed by other observers, who obtained essentially comparable figures<sup>21</sup> The curative dose of penicillin, whether in aqueous solution or oily suspension, varied with the number of injections into which treatment was divided. Penicillin in aqueous solution had to be subdivided into two to fourteen times as many injections as the oil-beeswax suspension to be equally effective. The superiority of the oil and wax suspension was particularly striking in schedules involving relatively large injections. The smaller the individual dose of penicillin, the less pronounced was that margin of superiority.

#### *Penicillin and Adjuvant Measures*

A large number of combinations of penicillin with heavy metals, arsenic, hyperpyrexia and other measures have been undergoing experimentation. The use of penicillin and bismuth in the treatment of experimental syphilis of rabbits has been found highly effective and safe with a minimum of reaction<sup>22</sup> A fat-soluble preparation of penicillin in the form of methyl ester was employed in the same fashion and seemed even more effective in its combination with bismuth, syphilis in rabbits required lower doses for cure, and the method was then applied to human beings, with equally satisfactory results<sup>23</sup> Prolonged periods of observation will be necessary in all these studies to ascertain long-term effectiveness. Confirmation of the value of combined therapy was not long in appearing, however, and the use of oxophenarsine hydrochloride combined with penicillin was likewise found of considerable value<sup>24</sup> A different type of bismuth salt was employed with just as satisfactory results. Oxophenarsine hydrochloride by both intravenous and intramuscular injection showed decided synergistic or adjuvant therapeutic effects in the penicillin treatment of syphilitic orchitis of rabbits. Bismuth subsalicylate is the most common salt of that metal to be employed in the treatment of syphilis. Its toxicity and therapeutic efficiency have recently been compared with those of two other bismuth compounds<sup>25</sup> The three bismuth compounds proved similar in therapeutic efficacy with generous margins

of safety. There is therefore no indication for the departure from general usage of the bismuth salicylate suspended in oil. All three types of bismuth preparations studied were mol for mol from one half to two thirds as active as Mapharsen in the treatment of experimental syphilis of rabbits. The margin of safety for the oily suspension of the subsalicylate was between six and eight times greater than that between effective and toxic levels of Mapharsen.

A new drug, Caronamide, is now being studied with the purpose of increasing penicillin plasma concentrations in man<sup>26</sup> This substance, when given orally to patients receiving penicillin, produced a physiologic and reversible inhibition of the excretion of this antibiotic, which increased the concentration of the penicillin in the plasma. Although there is not yet general agreement whether the maintenance of a constant level of penicillin plasma concentration is more desirable than the attainment of intermittent high levels, there is at least a need for high concentration of penicillin at certain times. Caronamide, when administered orally, elevates the penicillin plasma concentration from two to seven times, after either the oral or parenteral administration of penicillin, and should have great therapeutic usefulness in the treatment of conditions that require high penicillin blood levels. It is now being applied to the therapy of patients. Extensive laboratory investigation of the physiologic, pharmacologic, toxicologic and bacteriologic properties of Caronamide have justified its clinical use. The action of this drug is to inhibit the elimination of penicillin at the level of the renal tubules. The effectiveness of Caronamide is said to depend on a "substrate competition between penicillin, which is excreted by the tubules, and Caronamide, which is essentially refractory to excretion by that transport mechanism."

The therapeutic efficacy of penicillin *in vitro* has been shown to increase with temperature<sup>27</sup> Many syphilologists have been utilizing this fact in the combined treatment of neurosyphilis with penicillin and hyperpyrexia. A report has now appeared regarding the laboratory confirmation of this fact in experimental infections in rabbits<sup>28</sup> In the treatment of early syphilis in rabbits the therapeutic action of penicillin was strikingly enhanced by a simultaneous increase in body temperature, evidenced by the fact that the effective dose of penicillin was thereby reduced to one tenth of its usual level. The combination of fever with penicillin is neither feasible nor desirable, however, for the treatment of early syphilis in man. Penicillin therapy may be supplemented by bismuth or Mapharsen, which do not carry the risk of fever therapy and require considerably less expenditure of time and money. In neurosyphilis, however, the situation is quite different. penicillin alone may not suffice, and the

advantages of fever therapy are already well recognized. Whether the hyperpyrexia exerts its own effect or serves also to enhance the spirocheticidal activity of penicillin, their use in combination should yield results exceeding those hitherto obtainable.

### Experimental Reinfection

The question of reinfection vs. relapse has been a most controversial one since the advent of penicillin with its rapid eradication of lesions and apparent "cure" of early syphilis. Recurring evidence of clinically active disease after penicillin therapy has been variously interpreted as relapse or reinfection, depending upon the observers' evaluation of the history and symptoms. A relapse might thus be a treatment failure. On the other hand a reinfection could be used as a criterion of cure, or possibly of superinfection. A study of experimental syphilis in the rabbit has been conducted to determine what incidence of reinfection could be produced within ten days of the completion of adequate penicillin therapy.<sup>19</sup> Acute syphilis in rabbits was cured in three days with penicillin therapy, reinoculation was then attempted ten days after treatment had been completed. Twenty-seven per cent developed dark-field-positive chancres at the sight of reinoculation, and the remaining 73 per cent developed a symptomless infection confirmed by positive lymph-node transfer. Untreated rabbits with acute syphilis, reinoculated with a homologous strain of spirochetes at the same time period as the treated animals, did not develop clinical evidence of reinfection. It appears from this experiment (in which the second inoculation was introduced before the initial lesions had completely healed) that symptomatic or symptomless reinfection may take place before the disappearance of either the original clinical symptoms or the seropositivity of the host. This explains the so-called "ping-pong" syphilis, which has been noted in some patients with early syphilis treated with penicillin, in which a repeated interchange of infection occurs between two people with the same strain of *Treponema pallidum* (*Spirochaeta pallida*). The human body does not have time to produce a tissue immunity when the infection is eradicated so quickly. A symptomless reinfection may occur with a clinical and laboratory pattern resembling one of true serologic relapse in untreated animals or human beings. There is at least an immunity that lasts for a varying period and prevents reinfection in untreated cases.

### Penicillin Resistance

It has been suspected that penicillin-resistant strains of *Tr. pallidum* might appear. Earlier work with repeated culture passages through mediums containing substerilizing concentrations of penicillin

did not show evidence of increased resistance to penicillin.<sup>20</sup> Further experimental evidence has now appeared from work with syphilis in rabbits.<sup>21</sup> There was no evidence that *Tr. pallidum* acquired any resistance to penicillin after three consecutive passages through the testicles of rabbits treated with subcurative amounts of commercial penicillin. After the final passage the last group of rabbits was given a minimal curative dose of penicillin, and total cure was confirmed by lymph-node transfer. If this is true of the human disease it is exceedingly encouraging, since up to now almost every chemotherapeutic or antibiotic approach to human infection of any sort has sooner or later encountered resistant strains of organisms, regardless of the infection.

### Synthetic Penicillin

The complexity of processes required for the production of penicillin naturally led to attempts at synthetic development of this antibiotic. Synthetic penicillins have been produced independently in the United States and Great Britain as long ago as 1944.<sup>22</sup> Because of the obscurity of reaction mechanism, the synthesis at the present stage of development cannot be used as proof of the structure of penicillin. Improvement in the methods of synthesis have not progressed sufficiently to make commercial production practicable. It may be possible, however, to make new penicillins, which might possess even more desirable therapeutic properties.

### Streptomycin

With the advent of another wonder drug, streptomycin, it was natural to expect quick investigation of its possible effect on syphilis. It was found that the smallest amounts of streptomycin that cured syphilis in rabbits were more than three thousand times greater than the quantity of penicillin G required for effective sterilization of the infection.<sup>23</sup> The use of streptomycin for syphilis is obviously impracticable. Subsequent study of the same problem by other investigators was even less encouraging.<sup>24</sup> Still further work pointed to the possibility that streptomycin has no actual effect on syphilis.<sup>25</sup>

### Prophylaxis

In spite of education, various public-health attempts at control measures and new effective methods of therapy, the vagaries of human nature will probably always leave a place for prophylactic measures in the prevention of syphilis. The latest attempts to create effective prophylactic measures have been concerned with the use of propylene glycol solutions and ointments of various arsenox-

ides<sup>36</sup> Aqueous solutions in dilute soap were also employed. All these preparations had an encouraging prophylactic effect in preventing syphilis in rabbits, the ointments being the least useful regardless of the type of base employed. When infection was attempted through normal skin the soap solutions were highly effective prophylactic agents. If direct access was provided to the blood or lymph channels, all the prophylactic measures were largely ineffective. The application of these principles to the prophylaxis of the disease in men would encounter so many variables that an assay of their value would be exceedingly difficult. The length of time during which the organism might remain accessible to the prophylactic drug is unknown. The infectiousness of the exposure would vary. The time interval between the exposure and the use of prophylaxis, as well as the skill of the prophylactic application, would make the results of dubious significance.

### Staining Method

Numerous methods of staining *Tr. pallidum* have been reported in the past, but most of these require techniques that are not readily available and often too complicated for convenient use. A reasonably quick staining method that may be more generally applicable has been described.<sup>37</sup> The entire process is said to take only one minute, but the description will not be repeated here. Its usefulness is somewhat limited since dark-field examination is generally available and is usually more reliable. In some cases in which exudate is profuse and relatively uncontaminated serum cannot be obtained, staining methods would be of use.

### IMMUNITY IN SYPHILIS

Human beings do not possess natural resistance to syphilis, but some degree of immunity develops in man as a result of syphilitic infection. The mechanism of the defense process is still unknown. It is probably a tissue or cellular reaction, since the existence of humoral antibodies against syphilis have not been demonstrated. Numerous attempts to induce active or passive immunization against syphilis in man and animals have failed to produce any significant results. The relation of the positive serologic reaction to the organism's capacity to produce antibodies against spirochetes is not clear. Immunity at any stage of the disease is never absolute, but only relative. Untreated infection with syphilis confers on the human being immunity that prevents natural superinfection but does not protect him against massive artificial superinfection. Intensive treatment of early syphilis is in all probability capable of curing the disease. Such treatment abolishes all immunity that is in the process of development but does not endanger the patient if

it is strong enough to eradicate the infection completely. Inadequate antisyphilitic therapy will seriously impair the natural defensive mechanism, and the patient will be left both without a cure and without defense. This often leads to neurorecurrences, therapy-resistant relapses and precocious tertiarism. One student of the problem believes that animals treated in the late stages are biologically cured and at the same time actively immunized because they were thoroughly infected for a sufficiently long time.<sup>38</sup> A patient might thus be completely cured and yet remain refractory to natural reinfection. The reinoculation test (reinfection) is not believed by others to constitute a reliable criterion of cure in treated animals.<sup>39</sup> A symptomless infection is held to be possible in these animals, and this could be determined only by removal of tissue from treated animals at appropriate intervals after cessation of treatment and inoculation of that tissue into normal animals. These writers further believe that immunity is a special form of allergic hypersensitiveness. It is claimed that the whole course of untreated syphilis can be explained on the basis of allergy. The chancre is thus regarded as an allergic defensive measure that marks the beginning of the organism's altered reactivity to reinfection. The cutaneous manifestations of secondary syphilis are also thought to be manifestations of an allergic defense mechanism. The tertiary stage of the disease frequently shows severe local manifestations, during a phase in which the number of spirochetes is small, and these events are regarded as signs of a high degree of allergy. It is possible that a new approach toward understanding the nature of immunity in syphilis will be possible if further study confirms the preliminary demonstration of complete sterilization by penicillin therapy of animals experimentally infected with syphilis.<sup>39</sup>

A study of the same problem in infected rabbits treated after periods of three or four months with arsenobenzol injections led to the conclusion that immunity cannot depend on the persistence of parasites but must be an acquired one that developed at least three months prior to the treatment.<sup>40</sup> Attempts at reinoculation, as well as tissue inoculations from the treated animals, were confirmatory. Only 3 per cent of the reinoculated animals developed clinical syphilis, and 6 per cent presented symptomless reinfection. It was further shown that the immunity persisted in varying degrees for approximately a year before it decreased appreciably. Still another author proposes the term "reactivation" for infections such as syphilis, in which an "immunoallergy potential" is all that remains of an infection and in which reinoculation does not produce reinfection or superinfection.<sup>41</sup> He believes that parts of the syphilitic process may be evoked by superinoculation in such cases, because the first course of events in an infection cannot be exactly repro-

duced while some degree of allergic state or immunity persists. It is further stated that in absolute cure neither spirochetes nor potential remain.

It is obvious that thorough disagreement if not confusion exists rather generally regarding the problem of immunity in syphilis. Perhaps the best lesson to be learned from this discourse is the fact that a small amount of treatment in early syphilis, which is inadequate to eradicate the infection, is worse than none. It will interfere with the body's own defensive mechanism, fail to eliminate the infection and leave the patient worse off than nature alone would have left him. Perhaps his untreated infection will be discovered at some later date during the so-called "hyposensitive phase," when it may be at least arrested by therapy, before he reaches the hypersensitive or allergic state in which the explosive tertiary tissue reactions take place.

(To be continued)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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#### CASE 34031

##### PRESENTATION OF CASE

*First admission* An eighteen-year-old girl was admitted to the hospital with dyspnea

Three years previously, following the death of her mother with pulmonary tuberculosis, she became run-down and developed cough, sputum and hemoptysis. An x-ray film showed cavitation in the right apex, and she was hospitalized in a sanatorium for two years. While she was at the sanatorium a good collapse was obtained by pneumothorax, and she gained weight and became symptom free. The pneumothorax was continued at intervals after discharge. Three months before admission, following a refill of air, she developed a persistent dry cough, fever and night sweats.

Physical examination revealed a well developed, well nourished girl with signs of fluid in the right side of the chest.

The temperature was 99 to 100°F, the pulse 90, and the respirations 20.

Examination of the blood and urine was negative. An x-ray examination of the chest showed a pneumothorax on the right, the fluid level lying opposite the seventh interspace posteriorly. The right lung was about three quarters collapsed, and no cavities were seen. The left lung field was clear. The heart was displaced.

A chest tap yielded purulent fluid. Ordinary aerobic and anaerobic cultures were negative, a guinea-pig inoculation was positive for tuberculosis.

The temperature and pulse subsided, and the patient was discharged eight days after admission. Pneumothorax was permanently discontinued.

*Final admission* (nine years later) The patient was readmitted because of dyspnea.

For many years she had felt well. She had married and had had a normal pregnancy. Two years before readmission she developed a lump in the right breast. A simple mastectomy was done at an outside hospital, and the pathological report was carcinoma (Grade II). She then received fourteen radium treatments. Six months later she noted a lump in the right axilla, and a complete axillary dis-

section was done. She made a good recovery and worked as a cook until four months before re-entry. At that time she began to have pleuritic pains in the bases of the lungs and shoulders, shifting from one side to the other, associated with a temperature of 100°F, cough with some expectoration of white material, anorexia, nausea and vomiting and weight loss. In the past month there was also rapidly progressive dyspnea, weakness, dizziness and a temperature of 98 to 101°F.

Physical examination revealed a well nourished, orthopneic woman. There were flatness and absent breath sounds in the lower half of the right side of the chest.

The temperature was 99°F, the pulse 110, and the respirations 20. The blood pressure was 134 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 11.5 gm and a white-cell count of 12,800, with 89 per cent neutrophils. The urine and stools were normal. A Congo red test showed 60 per cent retention of the dye in one hour.

An x-ray film of the chest showed the right lung expanded to only half the thoracic cage and covered by a thick layer of organized pleural exudate (Fig 1). Fluid and air filled the remaining portion of the chest cavity, the fluid level being at the ninth rib posteriorly. There was also considerable thickening of the parietal pleura. It seemed that only the upper lobe of the lung contained air, the remaining portion of the lung being drowned. The mediastinum was not displaced. The left lung was clear.

A thoracentesis was done, and 300 cc of thick, turbid fluid was removed. Ten days later the fluid had reaccumulated, and another 200 cc was removed. Ordinary cultures of this fluid showed no growth. Two weeks later the patient complained of a constant aching epigastric and left-upper-quadrant pain unrelated to food. Nausea and vomiting became more frequent. A large, poorly defined epigastric mass was palpated. A peritoneoscopy was unsuccessful because of omental adhesions to the liver. This operation was followed by subcutaneous emphysema and persistent drainage of ascitic fluid through the opening. A plain film of the abdomen showed little, if any, air in the peritoneal cavity, most of it being distributed through the various layers of the anterior abdominal wall. The soft-tissue contours of the belly were obscured. A gastrointestinal series showed a normal esophagus. The stomach was displaced anteriorly and to the left by an epigastric mass, which was in the position of the left lobe of the liver. No evidence of intrinsic disease of the stomach or duodenum was found. Three weeks later there was pain low in the back, radiating down both legs.

The patient lost ground rapidly. Prior to death she was slightly icteric and had a miliary pustular purpuric rash over the upper limbs and shoulders. She died five weeks after readmission.

## DIFFERENTIAL DIAGNOSIS

DR. DONALD S. KING This is the story of a woman of twenty-seven who had a wasting disease of four months' duration, and this disease ran a febrile course. On physical examination there were two important findings: pleural effusion on the right and an epigastric mass. There was a history of two wasting diseases—tuberculous empyema and possibly generalized tuberculosis, and cancer of the breast with possible metastases. Both diseases can cause pleural effusion and abdominal fluid.

Did she have tuberculosis? Did she have cancer? Did she have both? One has to examine the three parts of the story. First, let us take the course of the disease. I stress the fact that it was a febrile course, and I consider that fact important. Very often when one follows the cases of known metastatic carcinoma from the breast with pleural effusion, temperature enters the picture and we wonder whether we are dealing with infection and not with a growth, but I do not believe that a persistent temperature for four months, as I assume this to have been, is quite consistent with cancer alone. To my mind, however, the febrile course favors tuberculosis. At the end pain occurred in the back and was referred down the sciatic nerve, but I think that it is too late to call that definite spinal metastases from the breast, although that is a common complication with such cancer. The slight icterus at the end and the milium pruritic lesions on the shoulders, I think, can be explained on either basis, perhaps slightly better as tuberculosis than cancer, but they are of no great significance.

DR. TRACY B. MALLORY Dr. King, would you like to see the temperature chart?

DR. KING Certainly. It seems that the patient was running only a slight temperature. She came in with a temperature of 101°F. Following that it was almost always above 99°F., occasionally 100°F. At the end the rectal temperature was 99 to 100°F., and finally she had a temperature of 104°F. This does not support my thesis too well. It was not a really febrile disease. I expected the chart to show a swing from 99 to 101°F. But I still think that the fever is a little more consistent with tuberculosis than with cancer.

There are two points about the pleural effusion. In the first place, the fluid is described as definitely thick and turbid, and a thick, turbid fluid is the fluid of tuberculosis and not the fluid of cancer with metastases to the pleura. I do not remember ever having seen anything except a fairly thin, straw-colored or bloody fluid with cancer of the breast involving the pleura. There is no report of guinea-pig inoculation at that time. It was nine years previously that the patient was known to have definite tuberculous empyema. At that time the pneumothorax, which she had been carrying for three years, was discontinued. We do not know how many

times the chest was tapped after that, and we do not know whether the lung re-expanded. We assume that it did. We dread the tuberculous empyemas, which may come with artificial pneumothorax, and that is one of the reasons why at present there is a slight tendency away from artificial pneumothorax treatment. This girl had had it nine years previously, and it looks as if she developed tuberculous empyema again.

May we see the x-ray films?

DR. STANLEY M. WYMAN The fluid level is probably intrapleural, as the record says. There is con-



FIGURE 1

siderable collapse of the right upper lobe. The right lower lobe cannot be identified. It is probably almost completely collapsed. The right breast is missing. I do not see any metastases, and I do not see any evidence of hilar or mediastinal nodes. This is the film taken after the first tap. It shows that the fluid level has decreased. There is a thin rind over the lung and along the wall of the thoracic cage.

DR. KING There is no description of the film taken before the chest was tapped. After the tap the patient had a small hubble of pleural air. Where the pleural air was coming from after nine years is hard to say. She may have developed a bronchial fistula, following which she again developed tuberculous empyema. So far as this film is concerned, it does not offer much to differentiate tuberculosis and cancer, except that I can explain the pocket of air better on the basis of tuberculosis with bronchial fistula than by cancer with pleural metastases. After she had been tapped the pleura presented a

different appearance. I am interested in the terminology. Dr Wyman called this a "rind," by which he means the thick layer of pleural exudate, which would have been called a "thickened pleura" five years ago. During the war Dr Wyman saw the surgeons "peel" off these exudates and leave a rather shiny pleura beneath. Later there may be organization of the pleural exudate and a condition more like a real "thickened pleura." In any case I think that the x-ray appearance of the pleura, both visceral and parietal, is more consistent with tuberculosis than with pleural metastases from cancer. The patient was a good candidate for metastases to the pleura, and extensive pleural thickening may be the result in such cases, but so far as the clinical course and the x-ray film of the chest are concerned, I am still in favor of tuberculosis.

The third point for consideration is the epigastric mass. In the x-ray report this is described as an ill defined shadow displacing the stomach anteriorly and to the left.

DR WYMAN. I assume that the location anteriorly was determined by the fluoroscopist. The stomach is certainly displaced to the left on both films. I cannot outline the definite mass on the film, and I cannot outline the abdominal viscera well because of the overlying gas in the abdominal wall. The gas is best seen in the lateral view.

DR KING. I suppose that during the peritoneoscopy they pumped air as they usually do and pumped it outside rather than inside, because of the extensive omental adhesions. At least we are told that there were adhesions. I do not believe that this shadow is the liver, but I want you to tell me what it is.

DR WYMAN. I cannot say that it is not the liver. I am rather inclined to think that it may be a slender tongue of liver tissue. The diaphragm is not elevated.

DR KING. I would like to attach this shadow to this one here and call them both liver. Is that possible?

DR WYMAN. It is hard to say that it is not.

DR KING. You do not help me much. The mass is in the position of the liver. Both lobes may be enlarged. All we know is that there were omental adhesions around the liver, and a mass. If we accept the diagnosis of tuberculosis, a mass involving a good many retroperitoneal lymph nodes is a good possibility. After peritoneoscopy fluid drained out through the peritoneoscopic wound. On this account I think that I should incline again toward tuberculosis, rather than cancer. Ascitic fluid can certainly develop with cancer because cancer of the breast often metastasizes to the peritoneum and there is drainage through the peritoneoscopy tap or puncture holes. But the evidence seems better for tuberculosis than cancer. I am still on the fence in deciding whether the mass was the liver.

There are two or three things that I might mention in closing. Amyloid disease may come into this liver problem. Amyloid disease was obviously under consideration when the Congo red test was performed. The test in this case was, in my opinion, normal. I recently heard Amberson, of New York, say that unless 100 per cent of the Congo red is absorbed from the blood by amyloid tissue, the test is of no value. That is a strong statement, but I think that it is probably true in this case that the test was not positive. If this had been a large amyloid liver I think that it would have absorbed more than 40 per cent from the blood serum. Dr Reuben Schulz, who has had a great deal of experience with amyloid disease, states that 20 per cent of all patients with tuberculosis autopsied at Middlesex County Sanatorium show amyloid disease. At Lakeville, where there is more extrapulmonary tuberculosis with osteomyelitis and so forth, the percentage is much higher. I have not seen a case for a year and a half. If this woman had tuberculous empyema for nine years she must have been a good candidate for amyloid disease. But I do not believe that we have evidence for tuberculous empyema over that period. Finally, if I make this diagnosis of tuberculosis, I am obviously on the spot regarding tuberculosis in the lungs. There is nothing that I can see in either of these chest films that looks like tuberculosis. The lower lobe that is mentioned as being "drowned," I do not believe is a drowned lobe in the sense that one ordinarily uses the term—that is, bronchial obstruction with infection beyond the obstruction. It is more to my mind an atelectatic lobe. What do you say, Dr Wyman?

DR WYMAN. I agree.

DR KING. I shall have to make a diagnosis of generalized tuberculosis, for I do not believe that tuberculosis of the pleura alone caused the death. It must have spread beyond the pleura to involve the bronchi and probably the mediastinal and retroperitoneal lymph nodes. In spite of the x-ray film, I believe that there was bilateral pulmonary tuberculosis. Did the patient also have cancer? I am voting against it. There is no proof. I think that she was a good candidate for neoplasm, and I am willing to admit that there are all kinds of loopholes. Out in Denver recently I saw a note on the wall of the clinical amphitheater saying, "A man learns 10 per cent of what he hears, 30 per cent of what he reads, 50 per cent of what he sees, and 90 per cent of what he does." I am going to add that he learns 100 per cent of what he does wrong in these clinicopathological conferences.

DR WYMAN. I should like to go on record a little more clearly regarding the liver. I believe that it may have been enlarged.

DR KING. That does not to my mind make the diagnosis of cancer. Dr Amberson also says that he found a good many fatty livers along with amyloid disease. Is it true, Dr Mallory, that an en-

larged liver in amyloid disease is due to fat and not amyloid?

DR. MALLORY I have not seen it often, but I imagine that it might occasionally be true

DR. REED HARWOOD The patient had icterus

DR. KING Yes, at the end she had slight icterus I do not know how much stress to put on it If one goes down the list of findings and symptoms in generalized tuberculosis it includes icterus But it would not help in differentiation of the two

#### CLINICAL DIAGNOSES

Metastatic carcinoma  
Tuberculous empyema

#### DR. KING'S DIAGNOSES

Pulmonary tuberculosis  
Tuberculous empyema  
Generalized tuberculosis involving mediastinal and retroperitoneal lymph nodes

#### ANATOMICAL DIAGNOSES

(Carcinoma of breast.)  
Metastases to lungs, liver, axillary, mediastinal and retroperitoneal lymph nodes, ovary and vertebrae  
Chylous ascites and hydrothorax, right

#### PATHOLOGICAL DISCUSSION

DR. MALLORY Autopsy showed widespread metastatic carcinoma. That may or may not be the entire answer. The liver was very much enlarged and full of metastatic carcinoma. There was also a very diffuse involvement of the lymph nodes of the mediastinum and up and down the aorta and retroperitoneal area, probably including the area of drainage of the thoracic duct. At the time of autopsy there was turbid fluid in both the abdomen and the cavity in the right side of the chest. Our impression of that fluid was that it was pseudochylous rather than purulent. There were very few cells found. At the time of death a guinea-pig inoculation of the pleural fluid had not been reported. Therefore, we did not include it in the abstract. This morning we sacrificed the animals, and they were entirely normal. On the other hand the cavity in the right pleura was encapsulated with thick, almost acellular collagen, which was in turn lined with a cheesy type of exudate. We were not able to demonstrate any microorganisms on smears. There was no suggestion histologically of acute tuberculosis anywhere in the body. I think that the origin of the cavity was unquestionably a tuberculous empyema. The recent cavitation, however, was probably a mechanical phenomenon associated with blocking of the lymphatic channels and the accumulation of chylous material.

DR. KING So the "thick turbid fluid" was one place where I went astray. I assumed that it was purulent, but I was not told that it was purulent.

DR. MALLORY I did not see the fluid removed by thoracentesis. It is possible that it was purulent, but I suspect that it was similar to that which we saw a few weeks later at autopsy, which was definitely not purulent.

DR. KING Have you often seen cancer involving the thoracic duct?

DR. MALLORY No, it is apparently an unusual phenomenon. It is much commoner of course to see thoracic-duct occlusion from lymphomatous tumors.

DR. KING This was not cancer over the surface of the lung.

DR. MALLORY No, extensive cancer was present within the lung, especially in the lymphatic vessels. The right lower lobe — the one that appeared collapsed — was almost filled with carcinoma. In that lobe the cancer had invaded the bronchus. The gross picture of that area was not incompatible with primary cancer of the lung, but the rest of the pathological picture and the history ruled that out.

#### CASE 34032

##### PRESENTATION OF CASE

**First admission.** A twenty-one-year-old cook was admitted to the hospital because of cough, dyspnea and hoarseness.

Four months previously he developed a steady aching remitting pain that radiated to the shoulder and left arm and was unassociated with sensory or motor disturbances. It disappeared spontaneously about two months before entry, but he developed a deep chest cough, sometimes productive of white phlegm. The cough became more irritating, both day and night. In the last month he had progressive dyspnea on exertion and occasional night sweats. Two weeks before entry he developed persistent hoarseness and one week later noted intermittent pain in the right lower portion of the chest and some hemoptysis with the cough. The general condition remained good.

Physical examination revealed a well developed and well nourished man in no acute discomfort. He had obvious cough and hoarseness. The left leaf of the diaphragm was high and immobile, and in the base of the left lung the breath sounds were diminished, there were no rales. The trachea was in the midline. The superficial lymph nodes were not enlarged.

The temperature was 99°F, the pulse 90 to 100, and the respirations 20. The blood pressure was 138 systolic, 94 diastolic.

Examination of the blood disclosed a hemoglobin of 14.2 gm and a white-cell count of 15,000, with 84 per cent neutrophils. The blood nonprotein nitrogen, the total protein and a urine examination were within normal limits.

An x-ray film of the chest revealed an irregularly ovoid, soft-tissue mass in the anterior mediastinum,



which could not be definitely separated from the heart shadow. The mass projected more to the left, where its border was poorly defined. Areas of increased density radiated from the mass into the lung. The left leaf of the diaphragm was elevated and showed limitation of movement. The left pleural cavity contained a small amount of fluid. There was a mediastinal shift to the left on inspiration.

Bronchoscopy showed paralysis of the left vocal cord in abduction. The epiglottis was normal. The trachea was pushed to the right by an intrinsic mass on the left. The caliber of the trachea and the mucosa were essentially normal. The carina was pushed a little to the right, and was slightly widened and partially fixed. The right bronchial tree was normal. The left bronchial tree could be examined only for a distance of 3 cm beyond the carina because of fixation both laterally and medially.

An aspiration biopsy of the left side of the chest parasternally showed a few tumor cells considered to be carcinoma, but the biopsy was inadequate to warrant a definite diagnosis.

The patient was treated with 7200 r of x-ray therapy to the chest. The tumor regressed readily, and he was discharged.

*Final admission* (four months later). He was readmitted because of pain in the lower back radiating down the left leg to the ankle, which he had developed shortly after discharge from the hospital. He was given 1500 r of x-ray therapy to the lower spine, with questionable relief. Three weeks before entry he began to have weakness and numbness of the left leg, and two weeks later he began to have pruritus, most marked over the lower limbs. He lost about 10 pounds of weight in one month.

Physical examination revealed a well nourished man, with slight shortness of breath and hoarseness. The trachea was shifted to the left, and the breath sounds on the left were diminished. The left pupil was smaller than the right, and there was slight weakness of the left leg.

The white-cell count was 9100, with 83 per cent neutrophils. The urine showed a + test for albumin and had a specific gravity of 1.006. An x-ray film of the lumbar spine and pelvis demonstrated areas of rarefaction in the left ilium and pubic bones. In the chest there was enlargement and coalescence of the perihilar lymph nodes bilaterally, and marked elevation of the left leaf of the diaphragm.

The patient was treated with 3600 r of x-ray therapy to the pelvis and 1800 r to the chest. He vomited persistently and had a generalized Jacksonian seizure. He deteriorated progressively and died five weeks after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. LOWREY F. DAVENPORT. We are given the salient facts in this case. A malignant tumor was discovered in the anterior mediastinum and hilar lymph nodes of the chest, causing severe localized

pressure symptoms. Subsequently, it metastasized to distant parts of the body, leading ultimately to death within a period of less than a year. Our chief concern, then, is the nature of this tumor. Apparently, a presumptive diagnosis of carcinoma was accepted on the basis of the cellular findings in the chest fluid. These findings were admittedly insufficient to warrant a final diagnosis and were accepted as a working diagnosis for therapy. It may be well to review the data in chronologic order to see if a more acceptable differentiation can be made.

This twenty-one-year-old man had initial symptoms of pain in the left shoulder and arm. Two months prior to the first admission he developed a cough, followed later by dyspnea and occasional night sweats. By the time he was admitted there was hoarseness, which was due to paralysis of the left vocal cord. So far these symptoms are more consistent with a malignant lymphoma than with a primary bronchiogenic cancer. The malignant lymphomas involve hilar lymph nodes early and frequently cause early pressure symptoms. At the age of twenty-one this type of tumor is certainly more common than bronchiogenic cancer, intermittent and hectic fever is frequently associated with lymphoma, particularly of the Hodgkin type. However, we are told that the patient had had some hemoptysis just prior to admission. As a general rule lymphoma does not cause bleeding, and in contrast to bronchiogenic cancer it does not originate in the bronchial mucosa and rarely invades it. I know of no single case in which a sufficient amount of lymphomatous tissue has been obtained by bronchoscopy to make a definite diagnosis. The occurrence of hemoptysis, then, is more commonly associated with carcinoma than with lymphoma.

The physical findings give no help in the differential diagnosis at the time of the first admission. There was definite paralysis of the left vocal cord and left side of the diaphragm, which only substantiates the previous impression of a malignant tumor. The absence of enlarged superficial lymph nodes is of no diagnostic importance. We know that extensive lymphoma can occur without such adenopathy, but had it been present it would definitely be against the diagnosis of bronchiogenic cancer.

The bronchoscopic examination showed fixation of the left bronchial tree, but no intrinsic tumor was discovered. We have come to associate such fixation with malignant involvement of the mediastinal structures, but in the absence of a positive biopsy we can go no farther in differentiating various types of malignant processes.

The laboratory data, with the exception of the findings following aspiration biopsy, are of no help. Actually, in this clinic, we have had little experience in recent years with aspiration biopsy. In contrast to other clinics, it has been our usual procedure to advise exploratory thoracotomy rather than attempt

aspiration biopsy. This course has been followed because of the very same difficulty with aspiration biopsy that was encountered in this case. All too frequently insufficient tissue is obtained for diagnosis. There is also the real danger of spreading a malignant process that might otherwise be operable. In spite of this very definite lead — that "tumor cells considered to be carcinoma" were discovered — I am not yet willing to accept this statement at its face value. For the purpose of therapy, I should have agreed to large doses of x-ray radiation, believing that it was better to overtreat a lymphoma than to undertreat a cancer.

We can exclude a primary tumor elsewhere involving the chest secondarily since all the information points toward a malignant tumor originating in the chest. Among malignant tumors in the anterior mediastinum carcinomas of the thyroid gland and thymus are possibilities, but the location of this tumor was too low for these organs to be considered as sites of origin. The patient's age, the location of the tumor and the x-ray findings are against a diagnosis of bronchiogenic cancer. If we accept the aspiration biopsy as showing cancer cells, which could not be identified, we should consider a teratoma or malignant degeneration in a dermoid cyst as possibilities. Both such tumors occur commonly in the anterior mediastinum and can show a varying degree of malignancy.

However, a malignant lymphoma would best fit the entire clinical picture. This was a malignant tumor in a man of twenty-one, at which age a lymphoma is certainly the most common type of tumor. The early involvement of the hilar nodes, the initial symptoms of an irregular and unexplained fever and the widespread metastases are consistent with this diagnosis. When confronted by a single laboratory finding that does not fit the rest of the clinical picture, it is usually a safe rule to disregard it. This is even more valid when the test was admittedly "inadequate." At best our experience with aspiration biopsy has been so unsatisfactory that I should disregard this single finding and make a diagnosis of malignant lymphoma involving primarily the mediastinal lymph nodes, with widespread metastases elsewhere.

DR MILFORD D SCHULZ. Films of the chest made at the first admission show a mass presenting in the left upper mediastinum, continuous with the lung root, which cannot be separated from the vascular shadows. It has an irregular ragged margin, and in the periphery of the lung, there is a homogeneous area of increased density. The left leaf of the diaphragm is elevated. A tumor mass arising in the mediastinum or in the left lung root causing paralysis of the left phrenic nerve and some patchy areas of atelectasis in the lung would look like this.

Films made after x-ray therapy show some regression of the mediastinal mass but no return of the diaphragm to normal position. Still later films of the chest demonstrate probable enlarged lymph

nodes at the right lung root. A film of the pelvis made at the same time shows mottled areas of bone destruction involving the left ilium and pubis.

These findings are consistent with involvement by some malignant process. Bones involved by lymphoma look like this.

DR DAVENPORT. In spite of the aspiration biopsy suggesting that the process was a carcinoma, is it not true that the type of involvement in the bones of the pelvis is unusual with carcinoma and is much more consistent with lymphoma?

DR SCHULZ. Metastatic carcinoma of the bone can have almost any appearance, but in view of the patient's age, I should consider some type of lymphoma a very likely cause for this type of destruction. The appearance is consistent with that seen in lymphoma or reticulum-cell sarcoma.

#### CLINICAL DIAGNOSIS

Carcinoma of mediastinum

#### DR DAVENPORT'S DIAGNOSIS

Malignant lymphoma of mediastinal lymph nodes, with widespread metastases

#### ANATOMICAL DIAGNOSIS

*Malignant lymphoma, reticulum-cell sarcoma type, involving mediastinal and other lymph nodes, kidneys, adrenal glands, lungs, intestine, stomach, thyroid gland and bones*

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN. At post-mortem examination the mediastinum was a mass of fairly dense fibrous tissue in which could be found necrotic foci, apparently the remains of neoplastic lymph nodes. The x-ray treatment had really been effective, because the microscopical sections of most of the lymph nodes in this region showed no viable tumor.

Dr Davenport's prediction of widespread involvement was certainly borne out. The most striking finding was a pair of kidneys with a combined weight of 2300 gm — about six times the normal weight. They were enormous and were diffusely infiltrated with tumor, not as metastatic nodules such as one sees in carcinoma, but a generalized infiltration of the interstitial tissues deflecting and crowding out rather than destroying tubules and glomeruli. This accounts for the absence of renal failure. Similar infiltration had occurred in the lungs, adrenal and thyroid glands, stomach, small intestine and pancreas, as well as in many lymph nodes.

Morphologically, the tumor belongs to the malignant lymphoma group, and can be subclassified as a reticulum-cell sarcoma. The latter type of malignant lymphoma has a predilection for involving viscera either alone or in addition to lymph nodes and quite often misses the spleen, as was true in this case.

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## WATERS DEFILED

THE London *Lancet*,\* in a recent leading article, draws attention to the gross pollution of rivers and tidal reaches that exists today in Great Britain, practically unchecked. At Tynemouth, for example, the towns of Newcastle and Gateshead discharge each day approximately 30,000,000 gallons of untreated sewage into the tidal waters of the estuary—a mass of filth that requires several tides to clear away. The coastline of 150 miles between Liverpool and Barrow is the daily recipient of 200,000 gallons of crude sewage per mile, or about forty bucketsful per yard. In these waters people bathe by the thousands in hot weather, and from them shrimps and prawns are harvested for the nation's tables.

Interestingly enough, it is the British angler who is making the greatest outcry over this situation, for his salmon are disappearing, but Parliament will shortly have an opportunity to take cognizance of the situation when it considers the Rivers Boards Bill containing the recommendations of the Central Advisory Water Committee.

We have no superiority in this respect in our own country about which to brag, for we, too, have contaminated our streams and polluted our beaches without regard to health, decency or esthetic considerations. Harold L. Ickes in his column in *The Boston Traveler* of September 25, 1946, presents some figures that give an account of our stewardship over this land that spreads from sea to shining sea.

"More than 3400 cities and towns," he writes, "inhabited by 29,000,000 persons discharge into our waterways a volume of  $2\frac{1}{2}$  billion gallons of raw sewage plus  $3\frac{3}{4}$  billion gallons of industrial waste each day. The annual economic loss resulting from water pollution has been variously estimated at from a hundred million to a billion dollars."

Massachusetts made at least a start in the control of water pollution in 1945, when the Legislature authorized the Department of Public Health to prescribe rules and regulations "to prevent pollution of lakes, ponds, streams, tidal waters and flats and tributaries thereto." In certain instances it has been necessary to prosecute recalcitrant offenders before health hazards could be prevented and nuisances abated. In others, industrial wastes had become so obnoxious that living conditions in the vicinity were unbearable, and even the paint on buildings was discolored by gases containing hydrogen sulfide.

In 1947 further remedial measures were taken with the passing of legislation in Massachusetts, Connecticut and Rhode Island authorizing the ratification of a proposed compact between these states and the other New England states for the abatement of existing pollution and the control of future pollution in interstate waters. Putting these measures into execution will be slow, however, because of the costs involved and the scarcity of labor and materials for the construction of treatment works.

\*Leading article. Filthy rivers. *Lancet* 2 58, 1947

## VOIUNTARY HEALTH AGENCIES AND THE NATIONAL HEALTH COUNCIL

THE need for co-ordination and co-operation among voluntary health agencies particularly at the community level, has long been recognized. A cogent statement of proposals for greater efficiency that also contains an analysis of the problems and opportunities inherent in this phase of public health<sup>1</sup> was recently adopted by the National Health Council as a guide in the future development of its activities. If properly carried out any program based on the principles advocated in this memorandum should go far toward lightening the burden of illness, accident and premature death and, incidentally, toward eliminating the ever-present bugbear of governmental interference in medicine and public health. Proposals directed toward the attainment of such a goal merit the careful attention of all members of the medical profession.

The essential features of a local health council are defined as follows: representation of all operating health agencies in the community, both official and voluntary, continuous opportunity to study health needs and to assess health problems and work together on their solution, and an atmosphere of co-operation and tolerance for all members. The unified support of all voluntary agencies combined in a council is held to offer a great advantage to local health departments.

Existing health agencies struggling with identical problems will welcome advice (but not dictation) from a national source that is familiar with successful public-health methods throughout the country. Therefore, the closest co-operation of function among all health organizations is urged, but the idea of interfering with methods of fund raising or merging the functions of various agencies at the national level is rejected. The role of the National Health Council in this scheme for more efficient operation is regarded as vital, and it is recommended that the Council, which already comprises representation of such major organizations as the National Tuberculosis Association, American Red Cross, American Cancer Society, American Public Health Association and National Organization for Public Health Nursing,<sup>2</sup> be expanded to include

the Health Section of the Office of Education, the National Foundation for Infantile Paralysis, the American Medical Association (formerly a member), the American Hospital Association and other professional groups. Other recommendations include the establishment and expansion of a central statistical service and provision for a library and information service, since the National Health Council is not only in an advantageous position to observe and evaluate reports from all parts of the country and to suggest promising directions for further investigation but also especially fitted to stimulate sociologic and administrative research, which has lagged behind the more basic scientific investigations.

The specific proposals are based on the conviction that permanent progress in public health can best be achieved if people are helped to recognize and to solve their own health problems. The cordial attitude of the public toward health guidance and health agencies, the existence of more numerous and more competent bodies of health workers than ever before and the advantage of modern technique and scientific advances are considered to offer an unprecedented opportunity for constructive efforts to attain the goal of optimum health for the greatest number of people. The guiding principles proposed for the staff of the National Health Council are as follows: "field work, counselling and co-operation within and without, decentralization at every opportunity, focusing on problems, not on personalities, receptiveness to new ideas and to local viewpoints, suggestion rather than oracularity, a viewpoint broad enough to encompass the special interests of all health agencies, both voluntary and official, realization that many local health agencies are doing superior work and can contribute much to the national agencies."

Dr W P Shepard, author of these proposals and president of the National Tuberculosis Association, deserves the highest praise for a clear and constructive outline of public-health needs. The recommendations, essentially, apply the principle of the Community Fund to all matters pertaining to health. The progress of the National Health Council in forwarding the implementation of these suggestions will be closely watched by physicians and laymen alike, for the stake involved — maintain-

nance and improvement of health by democratic means — is vital

#### REFERENCES

- 1 Shepard, W P Unpublished memorandum to National Health Council, dated August 1, 1946
- 2 Medical News National Health Council expands program *J A M A* 133 639, 1947

#### "THAT THESE HONORED DEAD"

A FUNERAL procession has begun this year that will consume five more before its ending Coming from the four quarters of the globe its various elements are converging on their homeland bearing the bodies of our dead of World War II

Congress has voted this posthumous repatriation and reburial, and the next of kin must make the decision whether to leave the body of the deceased where it was buried by his comrades or to bring it home for reinterment The soldier or the sailor cannot be consulted He has made his last decision on all matters earthly

The *Journal* published on November 13, 1947, a directive from the Department of Public Health regarding the technicalities of reburial in the Commonwealth, giving grim substance to this sentimental journey, and the relatives of more than 200,000 servicemen who lie buried in foreign soil have signified their desire to have the bodies returned There are those who feel that the deceased would wish to remain where he now is, others prefer that their relative shall rest in the homeland and this, too, is entirely fitting and proper

There may be many reasons given either for exhuming these unembalmed bodies and bringing them home for reburial or for leaving them in permanent United States military cemeteries abroad The ultimate reason is one of sentiment, whether the body shall lie in a grave that can be watched and tended by those of his own blood or rest in a bit of American soil in some other country — a sentiment once so fittingly expressed in the familiar words of Rupert Brooke "That there's some corner of a foreign field that is forever England"

However we may feel in this respect, there comes the thought that wherever "these honored dead" may lie, it is "for us, the living" still to show that "increased devotion to the cause for which they gave their last full measure of devotion"

Wherever they may lie, may we be stimulated to greater efforts to see that out of the destruction of war there shall come something better for those now living!

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#### THE NEW ENGLAND DENTAL JOURNAL

The *New England Journal of Medicine* welcomes into the ranks of scientific journalism the *New England Dental Journal*, as the official publication of the six New England dental societies

The *New England Dental Journal*, a logical successor to the *Massachusetts Dental Society Bulletin*, which has been in publication since 1924, is making its bow with the new year Its publication will be in the hands of a representative committee composed of an editor from each New England state, under the two-year chairmanship of Dr Cedric F Haring, of Brookline, Massachusetts Dr Haring has been editor of the *Massachusetts Dental Society Bulletin* since January, 1945

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#### MASSACHUSETTS MEDICAL SOCIETY

##### DEATHS

BAILEY — Karl R Bailey, M D, of Jamaica Plain, died on December 21 He was in his sixty-first year

Dr Bailey received his degree from Tufts College Medical School in 1910 He was deputy health commissioner for the City of Boston and was a former member of the Massachusetts Medical Society

His widow and two daughters survive

McDONALD — Ray T McDonald, M D, of Medford, died on December 5 He was in his sixty-second year

Dr McDonald received his degree from Tufts College Medical School in 1918 He was senior medical officer at the Lawrence Memorial Hospital, Medford, and a fellow of the American Medical Association

His widow, a son, a daughter and a brother survive.

MacGRAY — Charles L MacGray, M D, of Needham, died on December 25 He was in his sixty-eighth year

Dr MacGray received his degree from Tufts College Medical School in 1914 He was a member of the New England Pediatric Society and a fellow of the American Medical Association

His widow, a son, five daughters, two brothers and six sisters survive

PHILLIPS — Charles H Phillips, M D, of Beverly, died on December 22 He was in his seventy-seventh year

Dr Phillips received his degree from Bowdoin Medical School in 1900 He was formerly assistant medical examiner for Essex County and was a fellow of the American Medical Association

His widow, two daughters and three grandchildren survive

PICKARD — Isaiah L Pickard, M D, of West Concord, died on August 12 He was in his eighty-first year

Dr Pickard received his degree from Harvard Medical School in 1896 He was a former member of the Massachusetts Medical Society

# MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## SCHEDULING IMMUNIZATIONS

So many considerations enter into determining the order and the age for the administration of immunizations that there is as yet no general agreement regarding an ideal plan.

The present recommendations of the Department concerning such schedules are given in Table I

Hospital, Harvard Medical School and Harvard School of Public Health

The unit is under the direction of Dr. Merrill C. Sosman, radiologist at the Peter Bent Brigham Hospital. Other personnel and equipment are provided by the Massachusetts Department of Public Health through grants from the Tuberculosis Control Division of the United States Public Health Service.

Through the use of 70-mm photofluorographic equipment, the cost of operation has been reduced

TABLE I Immunization Procedure Recommended

DISEASE	AGE AT TIME OF INITIAL DOSE	PRODUCT (ANTIGEN)	DOSE	INTERVAL BETWEEN DOSES	BOOSTER DOSE OR REIMMUNIZATION	REMARKS
Whooping cough	3-6	Pertussis vaccine	Three doses of plai vaccine (80,000,000,000 bacilli) alum precipitated vaccine (30,000,000,000 bacilli)	30	One dose 1 yr. later; repeated at 5-6 yr. plai vaccine (20,000,000,000 bacilli); alum precipitated vaccine (10,000,000,000 bacilli)	Vaccine may be combined with diphtheria toxoid; booster doses should be given when disease is prevalent.
Smallpox	3-6	Smallpox vaccine	One vaccination	—	At 5-6 yr. of age; every 5-10 yr. thereafter	Vaccine may be combined with any dose of pertussis vaccine; revaccination indicated when disease is prevalent.
Diphtheria	6-9	Diphtheria toxoid*	Three doses of 0.5 cc. and 1.0 cc.	21-30	One dose (0.5 cc.) at 3-6 yr. of age†	Booster doses should be given at shorter intervals when diphtheria is prevalent.
Tetanus	6-12	Tetanus toxoid	Two doses of 1.0 cc. each	30	Recall dose (1.0 cc.) 1 yr. later	Another dose indicated after each deep or contaminated wound.
Typhoid fever	(When advised by physician)	Typhoid vaccine	Three doses of 0.5 cc. and 1.0 cc.‡	7-10	One dose (0.5 cc.) annually in areas where needed†	Triple vaccine should be given to travelers.

\*Two doses, 30 days apart, should be used for alum-precipitated toxoid.

†For booster dose, 0.1 cc. intracutaneously can be used.

‡Three doses of 0.5 cc. each recommended by some.

§For adolescents and adults, the first dose of diphtheria toxoid should be 0.1 cc., the size of succeeding doses being gauged by the reaction from the first inoculation.

These recommendations will be amended as new knowledge on many points is brought forward.

If every family followed a schedule of this kind, these diseases would become of little importance in Massachusetts.

Because parents often neglect to have the immunizations done by their own physicians, boards of health have been compelled to organize community immunization programs. In such programs, departure from the recommended procedures must occasionally be made. The essentials, however, can easily be covered in these programs.

## HARVARD PUBLIC HEALTH CHEST CLINIC

The official opening on Friday, November 7, of the Harvard Public Health Chest Clinic, located in the former Huntington Memorial Hospital, now part of the Harvard School of Public Health, marked a new step in co-operative tuberculosis prevention. By pooling funds, equipment and personnel, the Harvard Public Health Chest Clinic was brought into existence to serve the Peter Bent Brigham Hospital, Boston Lying-In Hospital, Children's

to the extent that the project is economically feasible.

The objective is to provide routine x-ray examinations of patients and employees of the member hospitals, as well as students and employees of Harvard Medical School and Harvard School of Public Health.

Since it has been shown that the tuberculosis rate of patients in general hospitals is approximately twice that of persons in the ordinary population, it is hoped that the routine screening for tuberculosis as proposed in this program will prove an effective means of disclosing unrecognized cases and protecting the hospital employees, medical-school personnel and nurses.

## MISCELLANY

### NOTES

The following appointments to the teaching staff of Harvard Medical School were recently announced: René Tagnon of Brussels, Belgium (A.B. University of Brussels 1939, M.D. University of Liège Medical School 1943), research fellow in medicine; Albert Kam Tai Ho, of Honolulu, Hawaii (S.B. University of Hawaii 1937, M.D. Jefferson Medical

College 1942), assistant in laryngology, Raymond Frank Kuhlmann, of Milwaukee, Wisconsin (A B University of Wisconsin 1936, M D Washington University 1939), assistant in orthopedic surgery, Herbert Fanger of Brookline (A B Harvard University 1936, M D New York Medical College 1940), assistant in pathology, Arthur Burns of Brighton (S B Boston College 1922, M D Tufts College Medical School 1926), teaching fellow in radiology, Chun-Hsiang Liu, of Peiping, China (M B Ministry of Education, China, 1940, M D National Tung-Chi University Medical School Shanghai 1941, D T M Calcutta School of Tropical Medicine 1945), research fellow in physical chemistry, Robert Fernand Mouton, of Brussels, Belgium (S D Brussels Free University 1944), research fellow in physical chemistry, Hans Nitschmann, of Berne, Switzerland (Ph D University of Berne 1931), (Privatdozent University of Berne 1942), research fellow in physical chemistry, Charles Tanford, of Boston (A B New York University 1943, A M Princeton University 1944, Ph D Princeton University 1947), research fellow in physical chemistry, Eero Johannes Uroma, of Helsinki, Finland (M D University of Helsinki 1943, Privatdozent Sero-Bacteriologie, Helsinki, 1947), research fellow in physical chemistry, Luis Saenz-Arroyo, of Mexico, D F (S B Institut Franco-Anglais 1937, M D National University of Mexico D F), research fellow in neurology, Lloyd Irving Sexton, of West Newton (S B Tufts College 1939, M D Boston University School of Medicine 1943), research fellow in obstetrics, Harry Amerman Bliss of Buffalo, New York (A B Princeton University 1941, M D Harvard University 1944), research fellow in physiology, John Lu, of Nanking, China (V Sc West China Union University 1940, M D West China Union University 1945), research fellow in surgery, John Eric Richardson, of Leicestershire, England (M B London Hospital Medical College 1939, M S London Hospital Medical College 1941, F R C S London Hospital Medical College 1944), research fellow in surgery, Joseph Worcester Spelman, of Kent, Connecticut (M D Yale University 1944), research fellow in legal medicine, John William Raker, of Boston (S B Bucknell University 1937, M D Harvard University 1941), research fellow in biologic chemistry, and Ian Chester Jones, of Liverpool, England (B Sc Liverpool University 1938, Ph D University of Liverpool 1941), research fellow in dental science.

#### NATIONAL CANCER INSTITUTE OF THE UNITED STATES PUBLIC HEALTH SERVICE

Awards totaling nearly \$750,000 in National Cancer Institute grants have been announced in a report made public by Dr. Thomas Parran, Surgeon General of the United States Public Health Service. Altogether 46 grants for clinical and basic biologic research were given on the recommendation of the National Advisory Cancer Council, composed of outstanding authorities on cancer from various sections of the country.

For the first time in the ten-year history of the Council grants were given to scientists working outside this country. The two recipients were Dr. A. Lacassagne, of the Institute Pasteur in Paris, who received \$13,380, and Dr. L. Doljanski, of Hebrew University in Palestine, who received \$10,000.

#### AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS IN MEDICINE

Research fellowships in medicine, with stipends ranging from \$2200 to \$3200, have been awarded by the American College of Physicians to the following physicians, for the year beginning in July: Charles G. Campbell, of Vancouver, B. C., for studies of the basic physiology of certain cardiovascular problems (at McGill University Faculty of Medicine), Frank H. Gardner, of San Bernardino, California, for studies of the mechanism and clinical application of the osmotic fragility test (at the Thorndike Memorial Laboratory, Boston City Hospital), Samuel P. Martin, of Durham, North Carolina, for studies of bacterial metabolism (at the Rockefeller Institute for Medical Research, New York City), Peritz Scheinberg, of Miami, Florida, for studies of cerebral circulation and peripheral vascular flow in normal and hypertensive per-

sons (at Duke University Hospital), Lutfu Lahut Uzman, of Istanbul, Turkey, for studies of the isolation and characterization of brain proteins and their role in health, disease and senescence (at the Department of Scientific Research, McLean Hospital, Waverley, Massachusetts), and John M. Weller, of Ann Arbor, Michigan, for studies of the ionic patterns of intracellular fluids and their influence on enzymatic reactions and of acid-base balance in tissues other than skeletal muscle tissues (at the Department of Biologic Chemistry, Harvard Medical School).

#### INDUSTRIAL CONFERENCE ON ALCOHOLISM

The first Industrial Conference on Alcoholism will be held in the Morrison Hotel, Chicago, on Monday, March 15. Sponsored by the Chicago Committee on Alcoholism, the Conference has been designed to bring to the attention of industrial leaders throughout the country facts pertaining to the problem of alcoholic employees and to discuss ways and means of overcoming the problem.

The Conference has been divided into three parts. In the morning session the discussion will center around "The Problem."

The second session will be held at a special luncheon at which an outstanding authority on the subject will be the key speaker. The afternoon session will cover the subject "What To Do about the Problem."

Reservations for attending the technical sessions and the luncheon may be made by application in writing to Walter O. Cromwell, vice-president, Chicago Committee on Alcoholism, 816 South Halsted Street, Chicago 7, Illinois.

#### "THIS WEEK IN CHICAGO MEDICINE"

The Chicago Medical Society has inaugurated a weekly mimeographed publication entitled "This Week in Chicago Medicine," designed to keep the medical profession posted and to aid out-of-town physicians who wish to visit clinics, conferences, round tables or medical meetings in Chicago.

Any doctor planning a trip to Chicago may obtain copies of this bulletin by writing to the Chicago Medical Society, 30 North Michigan Avenue, Chicago 2, or by calling in person.

#### BOOK REVIEWS

*Hypnotism Today*. By Leslie M. Lecron, B. A., and Jean Bordeaux, M. A., Ph. D. With a foreword by Milton H. Erickson, M. D. 8°, cloth, 278 pp. New York: Grune and Stratton, 1947. \$4.00.

The expressed purpose of this book is to "demonstrate that hypnotism is a true branch of psychological science, and to aid in removing some of the last lingering traces of the esoteric which still cling to it." So far as the authors adhere to the topic of hypnosis they do well in presenting the historical background and in offering critiques of existent laboratory studies, but these critiques are for the most part empirical and subjective. However, the authors digress at great length, with frequent interjections from their own experiences, into summary descriptions of behavior abnormalities (nonpsychotic), depiction of systems of psychotherapy in present vogue and further ramifications into the emotionally fraught question, "In whose bailiwick lies psychotherapy? They make out a plausible case for hypnosis ancillary to psychoanalysis (nonorthodox).

In many respects this volume has merit in its suggestions for measuring depth of the hypnotic state, in pointing out various weaknesses in past studies and present application and in offering leads for future research. The excursions across other horizons create a fog through which the title subject looms only occasionally. The authors in their zeal become somewhat evangelical and lose effectiveness through this disunity. The book ends with observations and philosophical conjecturing on the present training of physicians (psychiatrists) and psychologists (clinical psychologists) and equivocating about definitions of psychotherapy and treatment.

The book is easily read, and when the authors adhere to the title they present suggestions from their empirical experience that may be of value in stimulating objective work with hypnosis. The volume contains one hundred and twenty-six references and an index.

*Diseases of the Chest. Diagnosis and treatment.* By Archibald R. Judd M.A., M.D. 8°, cloth 608 pp., with 140 illustrations. Philadelphia F A Davis Company, 1947 \$9.00

In his preface the author outlines the objective of this book as a concise, practical and systematic manual of diseases of the chest. He emphasizes the fact that he wrote it to fill the needs of the general practitioner, intern or medical student and not for the specialist. It is with this in mind that the reviewer has gone over the twenty seven chapters of this manual.

There are five parts that consider the anatomy and physiology of the thorax, a fairly exhaustive study of pulmonary tuberculosis, nontuberculous pulmonary suppurative diseases of the lungs and pleura as well as silicosis, neoplasms, fungous diseases and cystic disease and finally miscellaneous aids in diagnosis, including bronchoscopy, bronchography and various other laboratory aids.

The author has long been a recognized authority on diseases of the chest and has absorbed much of the enthusiasm and zeal in the study of bronchology and pulmonary diseases from his close associates, the Jacksons. As a result of this major interest of the Philadelphia group there has certainly evolved, in the past quarter of a century, a much better and clearer concept of the physiology, pathology and rational treatment of lung diseases. The author discusses the subject quite adequately with an excellent interpretation of the long background and his personal experience in lung diseases.

Unfortunately, books do not have a morning and evening edition. In this atomic age there is nothing more perishable than a book on practical treatment. Some of the procedures are outmoded before the book reaches the shelves of the bookstore. Thus the omission of streptomycin to the general scheme of therapy in pulmonary tuberculosis is bound to leave quite a vacuum. Undoubtedly streptomycin is here to stay, and the entire early treatment especially that of tracheobronchial tuberculosis and other tuberculous complications will have to be reconsidered. In the light of present knowledge the entire chapter on tuberculous bronchitis will have to be rewritten immediately.

Likewise the chapter on carcinoma of the lungs lacks the latest procedures of bronchoscopic aspirations and the newer staining methods which make early diagnosis possible in a much higher percentage of cases.

The place of lobectomy and pneumonectomy in pulmonary tuberculosis is much more clearly defined now in view of the newer armamentariums on the treatment of pulmonary diseases. The remarks presented above are not meant as a criticism of the book but point to the need of a new edition almost before the ink has had a chance to dry.

Aside from the few omissions outlined, the author has covered the ground of all chronic diseases of the chest in a very adequate and practical manner. The general practitioner will find it an excellent reference book and the medical student will find it very useful as a condensed manual of all chest diseases. It is certainly a welcome addition to the literature on diseases of the chest.

*Signs and Symptoms. Their clinical interpretation.* Edited by Cyril M. MacBryde, M.D. 4°, cloth 439 pp., with 74 illustrations and 6 plates. Philadelphia J B Lippincott Company, 1947 \$12.00

The title of this unusually well organized composite work defines clearly the objective of the authors—namely to impress the physician with the importance of understanding correctly the complaints for which the patient consults him. With such an understanding a careful clinical history not only will simplify the physical examination and the selection of specialized laboratory tests but also will determine in large measure the correct diagnosis and appropriate treatment.

After an introduction by the editor on the art of history taking and on the technique of interpreting symptoms there follow twenty six sections or chapters covering nearly the entire field of symptomatology. Because pain is by far the most common presenting symptom a third of the book is devoted to this subject in its various manifestations: head ache, sore tongue and mouth, thoracic, abdominal, back and joint pain and pain in the extremities. Next are taken up fever, fainting and convulsions, dyspnea, cyanosis, palpitation, cough and hemoptysis, edema and dehydration, anorexia, vomiting and hematemesis, constipation, diarrhea and melena, jaundice, itching and finally, nervousness and fatigue.

Because the list is so comprehensive it is surprising that symptoms such as vertigo, purpura and hematuria have not been included.

Each section is a finished monograph in itself, concise and well correlated with the rest. The mechanism of each major symptom is clarified by whatever bearing anatomy, pathology, physiology, chemistry or psychology may have on it, and its correlation with other symptoms and with physical and laboratory findings is emphasized. The text is illustrated with many charts, diagrams and photographs in black and white and in color. References follow each section. Local contributors are Sara M. Jordan and William G. Lennox.

All in all this comprehensive work fulfills well the objective of the authors to help the physician evaluate the signs and symptoms of disease so that he may reach a correct diagnosis.

*Concise Anatomy.* By Lindeu F. Edwards Ph.D. 4°, cloth 548 pp., with 324 illustrations. Philadelphia The Blakiston Company 1947 \$5.50

This book admirably fulfills its intention to teach the basic principles of human anatomy to students in fields ancillary to medicine, such as nursing and physical education. It supplants the previous text by the same author entitled *Anatomy for Physical Education*. Much new material has been added, and the author correlates the anatomy with physiology and other applied matters. Although it is concise and simply written, the volume is entirely scientific in its approach and is obviously directed to people at college level. The illustrations and format are both instructive and pleasing and the book can be heartily recommended for students in the fields mentioned above.

*Diseases of the Gallbladder and Allied Structures. Diagnosis and treatment.* By Moses Behrend, M.D. With a foreword by Thomas A. Shallow M.D. 8°, cloth 290 pp., with 110 illustrations. Philadelphia F A Davis Company, 1947 \$7.00

This book is a review of forty five years' experience in the medical and surgical management of diseases of the gall bladder, bile passages and pancreas.

In the chapter on interpretation of liver function tests the limitations of the tests and their optimal value during the course of jaundice and convalescence are not included. It is stated that the prothrombinogen in the urine is increased in hepatocellular jaundice. However in the reviewer's experience this urinary pigment may be present in low levels or absent during the acute hepatocellular jaundice and is increased amounts only at the onset or at convalescence of the disease, when bile pigment is present in large quantity in the intestine. This test is frequently not of much help during the height of the illness, because the severely damaged liver may not be capable of manufacturing bile pigments. Its outstanding value is in revealing the patency of the common bile duct.

The omission of the value of the simple hippuric acid test as an indication of dehydration in the preoperative preparation of the patient with cholecystitis was probably an oversight.

The statement that persistent hypoprothrombinemia in spite of adequate intramuscular administration of vitamin K is a differential point excluding obstructive jaundice in favor of acute hepatocellular jaundice is not valid. In a large series of both obstructive and acute hepatocellular cases the responses of hypoprothrombinemia to vitamin K were approximately the same. Persistent hypoprothrombinemia in spite of adequate vitamin K occurred in chronic parenchymatous hepatitis and was usually an unfavorable prognostic sign.

None of the function studies described have revealed liver damage in the presence of severe grades of congestive heart failure.

The potential danger of increased liver damage if sulfonamides are used in jaundiced patients is overrated. The low incidence of sulfonamide sensitivity makes the use of these drugs relatively innocuous.

Recommendation of the indiscriminate use of plasma in preoperative preparation without knowledge of the source of the plasma may well result in more cases of homologous serum hepatitis, some of which are fulminating.

Anatomic variations and recent operative procedures are very well illustrated. The diagnosis and treatment of cholecystitis and pancreatic diseases are well outlined.



## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Twenty-Four-Hour Variations of Gastric Function and Their Significance for Diagnosis, Prophylaxis and Treatment of Dyspepsia, Especially in Tuberculosis*. By Erik Forsgren, M.D., physician-in-chief, Svenshögen County Sanatorium, 4°, paper, 34 pp. Lund, Sweden: Hakan Ohlssons Boktryckeri, 1946.

This study is based on routine examinations of 120 sanatorium patients, who were divided into two main groups: those with homoacidity and those with heteroacidity. They were studied on the basis of correlation between gastric acidity and subjective symptoms of dyspepsia and the correlation of tuberculosis and gastric function. The development of achylia and anemia associated with tuberculosis and the significance of the twenty-four-hour variation of gastric function from both the diagnostic and the hygienic viewpoints are discussed at length. A section is devoted to the treatment of achylia, especially in tuberculous subjects. The paper concludes with a summary in which the author states that he believes that routine examination of twenty-four-hour variations of gastric function should be made if there are symptoms of peptic ulcer, indigestion, deficiency conditions or tuberculosis.

*The Years After Fifty*. By Wingate M. Johnson, M.D., professor of clinical medicine and chief of private diagnostic clinic, Bowman Gray School of Medicine, Wake Forest College. With a foreword by Morris Fishbein, M.D. 8°, cloth, 153 pp. New York: McGraw-Hill Book Company, Incorporated, \$2.00.

During the past few years a number of popular books have been written on the hygiene and management of old age. Dr. Johnson has added another to this growing series and seemingly has not been able to reach down to the level of the layman but has landed in the middle between the physician and the subject. The style is factual and not conducive to easy interesting reading. The short comments are more on the professional than on the lay level.

*A Manual of Fractures and Dislocations*. By Barbara B. Stimson, M.D., M.Sc.D., assistant professor of clinical orthopedic surgery, College of Physicians and Surgeons, Columbia University, and associate attending surgeon, Presbyterian Hospital and Vanderbilt Clinic, New York City. Second edition. 12°, cloth, 223 pp., with 98 illustrations. Philadelphia: Lea and Febiger, 1947. \$3.25.

This manual has been revised in the light of war experience and has been brought up to date especially in the field of treatment. It should prove useful for ready reference to student and practitioner alike.

*Advances in Pediatrics*. Volume II. 8°, cloth, 409 pp., with 84 illustrations. New York: Interscience Publishers, Incorporated, 1947. \$6.75.

This second volume presents eleven special monographs on pediatric subjects of diversified interest and should prove valuable to the physician, as well as the pediatrician. The subjects discussed include the etiology of congenital malformations, endocrine and other factors determining the growth of children, prematurity, physiologic hyperbilirubinemia, the prevention of recurrences of rheumatic fever, acute infectious lymphocytosis, treatment of purulent meningitides, virus diarrhea, atypical pneumonia, the role of fluorine in prevention and treatment of dental caries and chemotherapy, including penicillin, the sulfonamides, streptomycin and tyrothricin. The papers are well written and provide up-to-date information on the various subjects. The book is well published in every way and should be in all medical libraries.

*Psychiatric Research*. Papers read at the dedication of the Laboratory for Biochemical Research, McLean Hospital, Waverley, Massachusetts, May 17, 1946. By Cecil K. Drinker, M.D., Sc.D., Jordi Folch, M.D., Stanley Cobb, M.D., Herbert S. Gasser, M.D., Sc.D., LL.D., Wilder Penfield, C.M.G., M.D., Sc.D., F.R.S., and Edward A. Strecker, M.D., Sc.D. 8°, cloth, 113 pp. Cambridge, Massachusetts: Harvard University Press, 1947. \$2.00. *Harvard University Monographs in Medicine and Public Health*, No. 9.

The seven papers comprising this volume are written by outstanding authorities in their particular fields. Dr. Drinker writes on research at the McLean Hospital, Dr. Folch on biochemical problems related to psychiatry, Dr. Stanley Cobb on the integration of medical and psychiatric problems, Dr. Gasser, director of the Rockefeller Institute, on a protocol for a review of psychiatry, Dr. Penfield, of McGill University, Montreal, on psychical seizures, and Dr. Strecker, of the University of Pennsylvania on the psychobiology of psychiatric research. This volume should be in all medical libraries and in all institutions having to do with mental disease. The small volume is published in the usual fine style of the Harvard University Press.

## NOTICES

## ANNOUNCEMENTS

Dr. Max Ettenberg announces the removal of his office to 258 Harvard Street, Cambridge.

Dr. Stanley J. G. Nowak announces the opening of his office for the practice of surgery at 99 Commonwealth Avenue, Boston.

## GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, January 20, at 8:15 p.m. A symposium on "Recent Advances in Chemotherapy" will be presented. Dr. Chester S. Keefer will be chairman.

## PROGRAM

Treatment of Pneumonia and Meningitis, with Some Consideration of Modern Trends in Time-Dose Relations in Antibiotic Therapy. Dr. Maxwell Finland.

Antibiotic Therapy in Scarlet Fever and Diphtheria, with a Consideration of the Change in Bacterial Flora of Infections during and following Treatment. Dr. Louis Weinstein.

Role of Streptomycin in the Treatment of Urinary-Tract Infections, with a Consideration of Its Toxicity. Dr. William L. Hewitt.

## LOWELL LECTURES ON THE HOSPITAL IN CONTEMPORARY LIFE

The following lectures, which comprise the second half of a course of eight Lowell Lectures on the subject "The Hospital in Contemporary Life," will be given in the Lecture Hall, Boston Public Library, Copley Square, Boston, at 8 p.m. on the days indicated.

Tuesday, January 20. The Education of the Doctor. Dr. Oliver Cope.

Friday, January 23. How Medicine Grows and Its Relation to Science. Dr. Eugene M. Landis.

Tuesday, January 27. Unsolved Problems. Dr. Joseph C. Aub.

Friday, January 30. The Place of the Hospital in the Social Order. Dr. Nathaniel W. Faxon.

Tickets can be obtained by mail, in advance, from the Curator of the Lowell Institute, Boston Public Library, from the office of the Director, Massachusetts General Hospital, or at the door immediately before each lecture.

(Notices concluded on page viii)

NOTICES (Concluded from page 106)

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 22

- FRIDAY, JANUARY 23**  
 \*9:00-10:00 a.m. Rheumatic Fever from the Epidemiological and Preventive Points of View Dr David D Rotstein, Joseph H Pratt Diagnostic Hospital  
 \*10:00 a.m.-12:00 m Medical Staff Rounds. Peter Bent Brigham Hospital
- MONDAY, JANUARY 26**  
 12:00 m. Clinicopathological Conference. Margaret Jewett Hall Mt. Auburn Hospital, Cambridge.  
 \*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.
- TUESDAY, JANUARY 27**  
 \*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.
- WEDNESDAY, JANUARY 28**  
 \*9:00-10:00 a.m. The Tuberculous Structure Dr Francis M Thomson, Joseph H Pratt Diagnostic Hospital.  
 \*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital.  
 \*1:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater Children's Hospital.

\*Open to the medical profession.

- JANUARY-APRIL** Thirteenth Postgraduate Seminar in Neurology and Psychiatry Metropolitan State Hospital Page 348 issue of August 25.
- JANUARY 20** Greater Boston Medical Society Page 106.
- JANUARY 20 AND 21** American College of Surgeons. Commodore Perry Hotel, Toledo, Ohio. Page 930 issue of December 11.
- JANUARY 20, 23, 27 AND 30** Lowell Lectures on the Hospital in Contemporary Life. Page 106.
- JANUARY 26** New England Heart Association Page 72, issue of January 8.
- JANUARY 26 AND 27** American College of Surgeons. Andley Hotel, Atlanta, Georgia. Page 930, issue of December 11.
- JANUARY 27** Norfolk District Medical Society Page 72, issue of January 8.
- JANUARY 30 AND 31** American College of Surgeons. Oklahoma Biltmore Hotel, Oklahoma City Page 930 issue of December 11.
- JANUARY 30 AND 31** Conference on Normal and Pathologic Physiology of Pregnancy. Page 1004 issue of December 25.
- FEBRUARY 6** American Board of Obstetrics and Gynecology Page 36, issue of January 1.
- FEBRUARY 12** Stipping of Upper Femoral Epiphysis. Dr John A Reidy Pentucket Association of Physicians. 6:30 p.m. Haverhill.
- FEBRUARY 23-28** Postgraduate Assembly in Endocrinology Page 36, issue of January 1.
- MARCH 28-APRIL 4** American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler Boston.
- APRIL 19-23** American College of Physicians. Page xiii, issue of July 31.
- MAY 6-8** American Association for the Study of Golter Page xiii, issue of July 31.
- MAY 17-20** American Urological Association Hotel Statler Boston.
- MAY 18-22** American Association on Mental Deficiency Copley Plaza Hotel, Boston.
- MAY 25-27** Massachusetts Medical Society Annual Meeting Hotel Statler Boston.
- JULY 12-17** First International Poliomyelitis Conference Page 36, issue of January 1.

DISTRICT MEDICAL SOCIETIES

FRANKLIN

- MARCH 9**  
 MAY 11 Annual Meeting. Hotel Weldon.  
 All other meetings will be held at the Franklin County Hospital

MIDDLESEX EAST

- JANUARY 21**  
**MARCH 24**  
 MAY 12 Annual Meeting  
 All meetings will be held at the Bear Hill Golf Club.

WORFOLK

- JANUARY 27** Round Table Discussion Bleeding from the alimentary tract.  
**FEBRUARY 24** Obstetric and Gynecologic Night.  
**MARCH 23** Harvard Night.

PLYMOUTH

- FEBRUARY 19** Toll House Whitman  
**MARCH 18** Goddard Hospital, Brockton.  
**APRIL 15** State Farm, Bridgewater.  
**MAY 20** Lakeville Sanatorium, Lakeville.

WORCESTER

- FEBRUARY 11** Worcester State Hospital.  
**MARCH 10** Memorial Hospital.  
**APRIL 14** Hahnemann Hospital  
**MAY 12** Annual Meeting

Medical Advertisement



From where I sit  
by Joe Marsh

# Only Way to "Handle" Poison Ivy

*Every now and then, Doc Hollister gets a serious case of poison ivy—like the time Ma Hoskins couldn't play the organ—and I run a notice in the paper, suggesting folks check up on their places for signs of the weed*

That's all that's necessary. Everybody makes a careful check, and usually it's just a single patch that needs uprooting. Because vigilance keeps poison ivy down, just the same way it controls everything else.

*Take our Better Business Bureau or the Brewers' Program of "Self Regulation." The Brewers are anxious to keep undesirables out of the "field," so they keep a constant check on taverns selling beer. If they see any signs of "poison ivy," the offending tavern gets cleaned up or reported to law enforcement agencies.*

Naturally, the tavern keepers are anxious to co-operate. And as a result any "poison ivy" is a rare exception. Because, as I say, vigilance is a mighty effective control.

Joe Marsh

# It Can Happen Here



*Example of severe rickets in a sunny clime.*

**L**EST WE FORGET—we who are of the vitamin D era—severe rickets is not yet eradicated, and moderate and mild rickets are still prevalent. Here is a white child, supposedly well fed, if judged by weight alone, a farm child apparently living out of doors a good deal. This boy was reared in a state having a latitude between 37° and 42°, where the average amount of fall and winter sunshine is *equal to that in the major portion of the United States*. And yet such stigmata of rickets as *genu varum* and the quadratic head are plain evidence that rickets does occur under these conditions.

How much more likely, then, that rickets will develop among city-bred children who live under a smokepall for a large part of each year. True, vitamin D is more or less routinely prescribed nowadays for infants. But is the antiricketic routinely administered in the home? Does the child refuse it? Is it given in some unstandardized form, purchased from a false sense of economy because the physician did not specify the kind?

A uniformly potent source of vitamin D such as Oleum Percomorphum, administered regularly in proper dosage, can do more than protect against the gross visible deformities of rickets. It may prevent hidden but nonetheless serious malformations of the chest and the pelvis and will aid in promoting good dentition. Because the dosage is measured in *drops*, Oleum Percomorphum is well taken and well tolerated by infants and growing children.



## OLEUM PERCOMORPHUM WITH OTHER FISH-LIVER OILS AND VIOSTEROL

Potency, 60,000 vitamin A units and 8,500 vitamin D units per gram. Supplied in 10 cc and 50 cc bottles, and as capsules in bottles containing 50 and 250

**MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U.S.A.**

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## MEDICAL AND HOSPITAL CARE OF THE VETERANS IN MASSACHUSETTS\*

WINTHROP ADAMS, M D †

BOSTON

THE entitlement of veterans to hospital and outpatient care under laws and regulations administered by the Veterans Administration is a part of any consideration of provisions for and distribution of medical care in Massachusetts, since there are approximately 600,000 veterans of wartime and peacetime service residing within the Commonwealth. All of these, comprising about 14 per cent of the entire population, are potential beneficiaries of these laws and regulations.

These veterans, men and women, who have served in the military forces are entitled, under existing federal laws, to medical care, including hospitalization or outpatient service for the relief of disabilities incurred in military service. There is further provision that, even though the disability was not incurred in the service, they are entitled to hospital care in Government hospitals for any disability requiring such care, regardless of when incurred, provided that they subscribe to a statement that they are unable to pay for the service elsewhere and provided that beds in Government hospitals are available.

Thus, veterans fall into two categories of entitlement to medical care: those with service-connected disabilities, and those with nonservice-connected disabilities. Of the 600,000 veterans in Massachusetts, approximately 79,000 have disabilities adjudged as service connected. It must be appreciated that many of these disabilities, such as amputations and loss of sight and hearing, as well as residua of wounds, are more or less static and permanent and will require little, if any, medical attention. However, pulmonary, cardiac and various other organic diseases, as well as nervous and mental afflictions, will require hospital or outpatient care for an indefinite period.

Of interest to the medical profession, as well as the public at large, is the plan of the federal Government, through the Veterans Administration, to provide

for the medical care of veterans in the Commonwealth.

At the present time, in Massachusetts, the Veterans Administration is operating five hospitals, with 4797 beds, 3100 of which are solely for the care of the mentally afflicted, 498 for tuberculosis, and the remainder—about 1200—for general medical and surgical cases. These hospitals are as follows: West Roxbury (general, 382 beds), Bedford (neuropsychiatric, 1822 beds, including 85 for women), Rutland 496 beds for tuberculosis, Framingham, formerly the United States Army Cushing General Hospital (general, neuropsychiatric and tuberculosis, 1000 beds)—this is one of the seven centers for paraplegic patients, includes 52 beds for women and is one of the Veterans Administration centers for the rehabilitation of aphasic and neurosurgical patients, and Northampton, 1095 beds for mental cases. In addition, the Veterans Administration has access to 250 beds in other Government hospitals, including the United States Naval Hospital at Chelsea and the United States Marine hospitals at Brighton and Vineyard Haven. As of a recent date, a total of 4724 veterans were hospitalized in Veterans Administration and other Government hospitals in the Commonwealth, 2091 of whom were receiving care for service-connected disabilities, and the remainder—more than half, or 2633 cases—for nonservice-connected ailments. Only 155 patients were hospitalized in civil or state hospitals.

The plans for the immediate future for additional hospital construction provide for a 1000-bed general medical and surgical hospital in Boston and a 1000-bed neuropsychiatric hospital near Boston. Upon completion, during 1950-1951, this will provide a total of about 6700 beds in Veterans Administration hospitals in Massachusetts, with the probability that further additional construction will be required before the estimated peak load is reached—between 1965 and 1970.

Outpatient service is an integral part of medical care for veterans. During a recent month, 9008 veterans received one or more physical examinations, and 12,990 were treated on an outpatient basis,

\*Part of a symposium on medical care presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1947.

†Branch medical director, Veterans Administration.

either in established Veterans Administration clinics or by physicians in the community in which the veterans reside

The Veterans Administration has established outpatient clinics in Boston, Worcester, Springfield, Lawrence, Lowell and New Bedford, with 46 full-time physicians and 42 part-time physicians employed. In the hospital service in Massachusetts, there are 70 full-time and 108 part-time physicians, including consultants and attendings, 71 residents and 66 young medical officers detailed from the Army and Navy, making a total of 315.

Although outpatient medical service to entitled veterans is practically restricted to state lines, no such limitation applies to hospital service. In other words, Massachusetts veterans receive outpatient treatment at clinics operated by the Veterans Administration or by civilian clinics or private physicians within the Commonwealth, but the Veterans Administration hospitals serve a veteran population in a general area. For instance, no construction of hospitals for the mentally afflicted or the tuberculous in Rhode Island, New Hampshire or Vermont is contemplated, consequently, beds in the neuropsychiatric hospitals in Massachusetts—at Bedford, Northampton and the proposed new center near Boston—will be available for the care of mentally afflicted veterans from other states.

Regarding the so-called "home-town care of veterans" an unfortunate situation arose, because of misleading publicity that appeared in press releases when this plan was started in certain states, as in Kansas, Michigan and New Jersey. It led many physicians, as well as the veterans themselves, to believe that family physicians could provide any sort of medical treatment, at Government expense. The releases did not stress the fact that the Veterans Administration could pay only for the treatment of service-connected disabilities and that, except in emergencies, the veterans should obtain prior authorization for the service required. Furthermore, it was not made clear that the Veterans Administration must use its established clinics to full capacity, and that veterans may be referred to private physicians only when reporting to the Veterans Administration clinic would work a hardship, such as loss of employment, or because of conditions prohibiting travel. The implementation of this plan in many sections, and this has been applicable to New England, has presented many difficulties, including agreement between the Veterans Administration and the state medical societies concerning a satisfactory fee schedule and the method of carrying the overhead—that is, whether or not an intermediary, such as the Blue Shield or Blue Cross, would serve as such an agent.

Negotiations between the Veterans Administration and officials of the Massachusetts Medical Society, through the Massachusetts Medical Services, Inc., have resulted in the adoption of a reasonably

satisfactory schedule of fees for various medical services. It was agreed that the Massachusetts Medical Service, Inc., would serve as the intermediary at a nominal charge for overhead, to be paid by the Veterans Association. Under this plan, the Massachusetts Medical Service, Inc., would receive initial authorization for the examination or treatment of a veteran, or a group of veterans, in a given community. The Massachusetts Medical Service would then advise the veteran, furnishing him with a list of physicians in his community who had expressed willingness to participate and serve. The veteran would go to the physician of his choice, who would submit his bill to the Massachusetts Medical Service for payment.

Authorization for treatment would carry authorization to prescribe indicated medication. The prescription would be presented to a local pharmacy for filling.

However, after the consummation of a contract with the Massachusetts Medical Service, Inc., it was found that the enabling act did not permit its negotiation with a federal agency, and amendatory legislation was requested. Such legislation has not to date been enacted, owing to objections on the part of certain groups.

Accordingly, unless favorable legislation is forthcoming, the implementation of this "home-town care plan" through the services of an intermediary, such as the Blue Shield or Blue Cross, will be impossible, and it will have to be worked out in accordance with the Kansas Plan, which comprehends direct action between the Veterans Administration and each individual physician who may be authorized to examine or treat a veteran.\*

There is, of course, no sound objection to this procedure, except that there will be a certain delay in effecting payments to physicians, owing to the paper work required in expending appropriated funds, under rather complicated procedures of Government accounting. With an intermediary functioning and willing to assume responsibility for direct payment to participating physicians, payment would be received more expeditiously.

Over the years, since World War I, the question has repeatedly been raised how far the federal Government should go in furnishing medical and hospital care to those who have served in the military forces. There has never been any question of the Government's obligation to those who became disabled as a direct result of their service, and I assume that no serious objection can be raised to governmental provision for the care of the mentally afflicted and tuberculous, regardless of the time of incurrence of the disability.

After World War I and until 1924, the statutes governing veterans' relief provided only for compensation and medical care for disabilities actually

\*Since this paper was delivered the Massachusetts Medical Society has entered into a new agreement with the Veterans Administration providing for the delivery of medical service according to the Kansas Plan.

incurred in service. If those statutes were in effect at this time, the Veterans Administration would be obligated to provide hospitalization for about 35,000 veterans instead of 104,000, the number hospitalized at the end of a recent month, and in Massachusetts, 2090 instead of 4724.

The service-connected cases hospitalized at that time comprised 6800 general medical and surgical, 6000 for tuberculosis and 22,000 classed as neuropsychiatric, the majority of which were psychotic patients. Of the nonservice-connected group under hospital care, about 68,000 in all, 32,000 were classed as general medical and surgical cases, 5800 as tuberculosis, and 31,000 as neuropsychiatric. These are national figures, but practically the same ratios prevail in the several areas throughout the country. Projected into the future, until 1965, when the peak load will be reached, a bed requirement of 225,600, including 7500 for tuberculosis, 121,200 for neuropsychiatric cases and 96,900 for general medical and surgical cases, is estimated. Of this total, probably not more than 35 per cent of the beds will be occupied by veterans with service-connected disabilities.

In the time allotted, I have been able only to touch upon the high points of a federal medical service that provides for a potential load of approximately 14 per cent of the population of the Common-

wealth. Although the hospital service is available, under certain legal and regulatory restrictions, to the entire group, it must be recognized that outpatient care in regularly established Veterans Administration clinics or through private physicians is limited to service-connected disabilities, under existing laws. With the lapse of time, when the number of service-connected disabilities becomes more or less static, the requirement for outpatient care will show a downward trend. On the other hand, with the liberal provisions for hospital care, the demand for such care on the part of veterans will increase through the years. In anticipation of this increased demand, the Veterans Administration has estimated a requirement for 15,000 beds for veteran care in New England by 1965.

The possibility of further amendments of the laws to provide outpatient care for veterans for non-service-connected disabilities cannot be ignored. Continually over the years, since World War I, bills have been introduced before the Congress on this subject. To date, none have been enacted, but the trend is unquestionably in that direction. Such an amendment would have considerable bearing on the distribution of medical care in the Commonwealth and would most certainly require a much wider utilization of physicians on a part-time or fee basis than under existing procedure.

## SURGICAL ASPECTS OF BRONCHIECTASIS\*

JOHN W. STRIEDER, MD †

BOSTON

IT IS generally agreed that the definitive treatment of bronchiectasis is surgical and that most patients should be considered for lobectomy or pneumonectomy, although many may, after evaluation, be denied operation for a variety of reasons.

In 1941 Riggins<sup>1</sup> wrote "The morbidity and mortality of untreated and medically treated bronchiectasis is such that the physician who routinely advises young adults with operable bronchiectasis against surgery, is assuming a large responsibility and in all probability renders his patient a great disservice." Corroboration of this statement is obtained in several recent studies, one of the best of which is presented by Perry and King,<sup>2</sup> who, on the basis of follow-up examination of 400 patients, conclude that in twelve years the mortality in the nonsurgically treated cases was 26 per cent, 41 per cent of the patients dying within five years of onset and 15 per cent living twenty years or longer after

onset. In the fatal cases, 78 per cent of patients died directly of the disease. Some statistical evidence supports the view that patients who develop bronchiectasis before the age of ten do not live beyond the age of forty. Thus, of persons with the onset in the first decade, only 9 per cent were living at the age of forty or over, whereas the onset was in the first decade in only 15 per cent of the 59 patients who reached the age of forty or over. The operative mortality in 122 lobectomies of the modern type, performed by Churchill at the Massachusetts General Hospital on 116 patients, was 3 per cent. The working and living capacity of the living patients who could be traced was considered excellent in 67 per cent of the surgical group and in 38 per cent of the nonsurgical group. These authors find nonsurgical treatment to be only palliative and believe that, because of the steadily decreasing operative mortality, simple lobectomy may be advised without hesitation. Even with bilateral disease the risk in bilateral lobectomy — of course in two or more stages — is often not too great.

\*Part of a symposium on bronchiectasis presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1947.

†Associate professor, Boston University School of Medicine; surgeon-in-chief for thoracic surgery, Boston City Hospital and Mattapan Sanatorium; visiting surgeon in charge of thoracic surgery, Massachusetts Memorial Hospital.

Bradshaw, Putney and Clerf<sup>3</sup> studied 242 patients with bronchiectasis. Of these, 112 were living, and 59 had died from bronchiectasis or its complications.

Riggins<sup>1</sup> found the mortality in 85 cases of medically treated bronchiectasis, collected during ten years but with many of the patients observed for only three or four years, to be 14 per cent. It should be added that children stand thoracic operations exceptionally well, and lobectomy early in life is almost certain to obviate the hazards of bronchiectasis that such children must face if they grow to adolescence or adult life with nonsurgical treatment.

Averaging the figures given by various students of the disease, Hinshaw and Schmidt<sup>4</sup> estimate that less than 10 per cent of patients with severe bronchiectasis obtain a satisfactory result from any form of medical treatment, and conclude that the mortality within ten or fifteen years after the diagnosis is made is somewhere between 30 and 50 per cent.

The development of the modern technic of intralobar dissection and individual ligation<sup>5</sup> has further improved lobectomy as applied to bronchiectasis. Although occasionally it may not prove feasible or may even be impossible in cases of so-called "frozen hilus," because of dense fibrosis resulting from repeated exacerbations of pneumonitis, this technic materially reduces the postoperative complications of empyema and bronchopleural fistula. The advent and increasing availability of penicillin promises a further reduction in the incidence of postoperative empyema. At the Massachusetts Memorial and Boston City hospitals it has been used prophylactically, in many cases both intrapleurally and intramuscularly, as part of the preoperative and postoperative routine, with gratifying results.

Growing knowledge of the surgical anatomy of the detailed structures of the lung, refinements in bronchography and clinical experience have demonstrated that a lobe of the lung is actually made up of a cluster of bronchopulmonary segments. In this connection an important contribution was made by Churchill and Belsey<sup>6</sup> in 1939. They correctly prophesied that the bronchopulmonary segment would replace the lobe as the surgical unit of the lung. Although Nelson<sup>7</sup> had earlier suggested that the lungs are made up of eight lobes—two upper lobes, two middle lobes, the dorsal divisions of the lower lobes and the basal divisions of the lower lobes—it remained for Churchill and Belsey to demonstrate the actual clinical application of this anatomic configuration. They applied the principle of segmental pneumonectomy to resection of the lingula of the left upper lobe ("left middle lobe") by removing the posteromedial segment of the lingula; they also employed the technic in operations on the dorsal divisions of the lower lobes. Such contributions are of value since they point the way to greater conservation of normal pulmonary tissue in cases in which lesions are well localized in a bronchovascular segment of the lung.

## RESULTS OF SURGERY

No discussion of the operative treatment of a disease is complete without reference to the risks involved. Churchill's excellent figures, as reported by Perry and King,<sup>2</sup> were mentioned above. Bradshaw and O'Neill<sup>8</sup> report the results of surgical treatment of bronchiectasis in 76 patients whose disorder was mostly due to an unknown etiologic agent. One death occurred among the 24 patients with disease of the lower lobe and of the lower lobe and lingula—a mortality of 4 per cent. Among 26 patients in whom one lobe was removed but in whom disease was present in other lobes, there were 4 deaths, a mortality of 15 per cent, whereas in 17 patients who had two or more lobes removed there were 3 deaths, a mortality of 18 per cent, 11 of these patients had disease in other lobes. Maier<sup>9</sup> reports 64 cases in which pulmonary resections for bronchiectasis were performed. Lobectomy was done in 55 cases, and pneumonectomy in 9, with 1 operative death—a mortality of less than 2 per cent. Sellors et al.<sup>10</sup> report 100 cases of bronchiectasis operated on by three surgeons employing the individual-ligation technic. Closure of the bronchus was attempted by various means, but no perfect method was found and bronchial fistula of varying size developed in 42 per cent of cases. This is a considerably higher incidence of fistulas than that of most thoracic surgeons in this country. There were 8 deaths, 4 occurring within one month and 4 from four to nineteen months after operation.

Kay and Meade<sup>11</sup> state that pulmonary resection for chronic sepsis with present-day technics, anesthesia and chemotherapy is a safe procedure and can be recommended without hesitation. In 100 cases in which they performed lobectomies, there was only 1 death—an operative mortality of 1 per cent, which compares favorably with that from any other operative procedure.

In a series of 72 patients with unilobar, multilobar, unilateral or bilateral bronchiectasis on whom 93 operations were performed at the Boston City and Massachusetts Memorial hospitals there were 7 operative deaths, a case mortality of 9.7 per cent or an operative mortality\* of 7.5 per cent.

An analysis of the deaths reveals that there were 4 deaths occurring within ten days of operation: 1 of surgical shock twelve hours after left-upper-lobe tourniquet lobectomy, 1 of sepsis and open pneumothorax ten days after left-lower-lobe tourniquet lobectomy, 1 of atelectasis and pneumonitis eighty hours after tourniquet lobectomy of the right middle and lower lobes in a bilateral case, and 1 death on the operating table of tension pneumothorax at the conclusion of a right pneumonectomy. Three deaths occurred forty to eighty days after operation: 1 of *Bacillus suispestifer* (*Salmonella*

\*"Operative mortality" is defined as the percentage of deaths directly attributable to operation.

*choleraesuis*) bacteremia forty days after left-lower-lobe tourniquet lobectomy, 1 of nephrosis and chronic empyema eighty days after the completion of bilateral lobectomy, and 1 of massive hemorrhage from a chronic empyema fifty-two days after completion of bilateral dissection of four lobes

In addition there were 2 deaths from brain abscess eighty-one days and one hundred and twenty-one days respectively after lobectomy in patients who had been discharged from the hospital after the original operation. Both were unilateral cases—1 a dissection lobectomy, and 1 a tourniquet lobectomy. There was also 1 death from massive hemorrhage eighty days after a tourniquet lobectomy of the right middle and lower portions, the patient having been discharged from the hospital after operation.

Of the 41 unilobar cases, in which the total mortality was 4.8 per cent, tourniquet lobectomy was performed in 12, with 2 deaths (a mortality of 16.6 per cent), and dissection lobectomy in 29, with no deaths.

In the 15 unilateral multilobar cases there were 8 bilobar lobectomies with no deaths, and there were 7 pneumonectomies with 2 deaths, or 28.5 per cent.

A survey of the 16 bilateral cases reveals that 7 were completed with 2 deaths (28.5 per cent), in 9 cases in which only the first side was operated on, 1 patient died (11.1 per cent). The total mortality in these cases was thus 18.7 per cent.

Regarding the extent of the bronchiectasis, which can be accurately determined only by adequate bronchograms, I agree with Alexander,<sup>12</sup> who believes that surgery is the treatment of choice for patients whose lesions are restricted to one lobe, to the right lower and middle lobes, to the left lower lobe and lingula ("left middle lobe") or, in some cases, to all the lobes of one lung (total pneumonectomy), to one lobe of each lung or to two lobes of one lung and one lobe of the other (bilateral lobectomy).

Bilateral lobectomy, in stages, has frequently been performed for bronchiectasis. It is routinely considered when the surgical program of suitable bilateral cases is planned. Churchill<sup>13</sup> reports 6 cases, with 1 death. I have performed bilateral excision in 7 cases, with 2 deaths. As might have been expected, however, and as borne out in Bradshaw and O'Neill's<sup>8</sup> report and the figures cited above, bilateral lobectomy is associated with a considerably higher mortality, since it subjects the patient to two major operations. Moreover, the postoperative period after the first lobectomy is rendered more hazardous because the patient must convalesce with disease remaining in one or more lobes.

#### NONSURGICAL MEASURES

Although the present safety of pulmonary lobectomy has solved the problem of treatment for approximately half the patients with bronchiectasis, the other half are, for a variety of reasons (particu-

larly because of extensive bilateral lesions), not suitable for the operation. Alexander<sup>12</sup> has discussed nonsurgical methods of treatment that, if properly and faithfully carried out, can effectively alleviate the distressing symptoms of the disease in a large majority of patients.

Postural drainage is the most valuable of the nonsurgical therapeutic measures. Every bronchiectatic patient should have at least one bronchoscopic examination, not only because some undetected important intrabronchial lesion may be discovered but also because the aspiration of secretions and the chemical shrinkage of the bronchial mucosa often bring about improvement in the symptoms.

Penicillin is of no permanent value in the treatment of advanced bronchiectasis, but if the organisms are sensitive it is of considerable benefit in preparing the patient for operation. It frequently decreases the cough and sputum and increases the sense of well-being, occasionally, it changes the character of the sputum. It is also of value in the treatment of the recurrent pneumonic episodes, as well as in decreasing the amount of sepsis and toxicity during the interval stages.

In the average case of bronchiectasis after penicillin is discontinued the symptoms soon recur. Pulmonary resection should not be withheld when indicated because of the false sense of security resulting from temporary benefit.

#### COMPLICATIONS

##### *Putrid Empyema*

Infection of the pleural cavity by a mixed flora is a not infrequent complication of bronchiectasis. The common organisms found are the anaerobic streptococcus and the fusospirochetal group. Acting in symbiosis, they give rise to a pleuritic exudate, which has been variously termed "foul," "stinking" or "putrid" empyema. In many cases actual perforation of an abscess cannot be demonstrated, and it may be assumed that the infection of the pleural cavity results from the rupture of microscopic subpleural abscesses, or perhaps by actual passage of the organisms across the visceral pleura via the subpleural lymphatic vessels, which has been shown to be operative under similar circumstances by several workers.<sup>14, 15</sup>

Whatever the mechanism involved, when the complication of putrid empyema occurs it must be considered, under most circumstances, an acute surgical emergency, in contradistinction to empyemas of ordinary pyogenic origin.<sup>16</sup> This is particularly true when a perforation assumes a valve-like action, and the problem of tension pneumothorax is added to that of the infection. In these cases only prompt decompression by surgical means can avert a catastrophe.

Even if there is no pyopneumothorax, the almost immediate effect of a virulent pleural infection of this type is frequently that of profound peripheral



vascular collapse, which clinically may be indistinguishable from surgical shock. If the diagnosis is suspected, it can be confirmed at once by thoracentesis and the aspiration of putrid, thin pus. When such a finding is made, surgical drainage, amply wide and open, must be undertaken forthwith. Strieder and Lynch<sup>16</sup> have shown that when prompt open drainage is established in putrid empyema, whatever its cause, the mortality drops from the rate of approximately 50 per cent prevailing when less drastic measures are used to about 14 per cent.

### Extension of Infection

Extension of the infection, either directly into the contiguous lung parenchyma from bronchiectatic abscesses or by bronchogenic dissemination into the same or a contralateral lung, is a common cause of death in bronchiectasis. In many cases this is due to the inexorable progression of a virulent infection in a host whose tissues offer inadequate resistance. In others, the difficulty stems from the impaired efficiency of the cough mechanism, as a result of which the copious, infected secretions bathing the tracheobronchial tree are not expelled. If a patient is unwilling or unable to cough efficiently because of debility or postoperative pain, frequent intra-tracheal catheter suction or bronchoscopic aspiration of secretions may suffice to tide him over the critical period until the cough mechanism is again functioning normally. Loss of effective ciliary action by the bronchial mucosa, which normally tends to lift secretions away from the pulmonary periphery, undoubtedly contributes to stagnation of secretions and their gravitation into the alveoli.

It is therefore of the utmost importance, both preoperatively and postoperatively, to employ all the available measures (forced cough, postural drainage, catheter suction and bronchoscopy) to promote evacuation of secretions and to prevent stagnation and gravitation to uninvolved portions of the lung.

### Metastatic Brain Abscess

Metastatic brain abscess frequently occurs as a complication of thoracic suppuration, in my own experience it has been uniformly and rapidly fatal. In a recent comprehensive paper, Collis<sup>17</sup> states that only 2 recoveries have been recorded after surgical drainage of brain abscesses secondary to thoracic disease. In his series, this cerebral complication occurred in 4.5 per cent of cases of lung abscess and accounted for 20 per cent of the mortality from lung abscess. There is also some evidence that its incidence has risen with the increase in operative procedures in thoracic suppuration. The experience of Collis is in accord with that discussed above in the over-all mortality for 93 operations for bronchiectasis. Of the total of 10 deaths (7 operative), 2 resulted from brain

abscess and occurred eighty-one and one hundred and twenty-one days respectively after operation.

### Hemorrhage

Hemorrhage is not an unusual complication of bronchiectasis. When it occurs before operation, as hemoptysis, it is usually mild, but it may at times assume alarming, although rarely fatal, proportions. Frequent hemoptysis is a definite indication for surgery in patients in whom there is, at the same time, no contraindication.

As a postoperative complication of tourniquet lobectomy hemorrhage was a dreaded and, when it occurred, rapidly fatal incident. It resulted from imperfect hemostasis of the lobar or pulmonary pedicle or from latent sepsis with delayed erosion of a large vessel of the pedicle. Fortunately, the modern dissection-ligation technique, whereby the hilar vessels of the lung or lobe are individually treated, has to a large extent obviated this complication.

### SUMMARY

The majority of patients with bronchiectasis should be considered for lobectomy or pneumonectomy although many may, after evaluation, be denied operation for a variety of reasons.

The operative results of 93 operations on 72 patients who had bronchiectasis are discussed.

The major complications of bronchiectasis are briefly reviewed.

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## MECHANISMS UNDERLYING PULMONARY AND CARDIAC COMPLICATIONS OF ELECTRICALLY INDUCED CONVULSIONS\*

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THE changes in pulmonary function observed during electrically induced convulsions account for the development of atelectasis and, more rarely, lung abscess in patients receiving electroshock therapy. A convulsion induced by electric shock is ushered in by maximal forced expiration, which is then maintained throughout the seizure.<sup>1-3</sup> Roentgenograms made at the height of the tonic phase of

During the seizure profuse salivation occurs, apparently as a consequence of autonomic stimulation, in addition it is possible that the marked elevations in blood carbon dioxide tension<sup>3</sup> and blood lactic acid<sup>4</sup> that have been noted stimulate increased secretion of the salivary glands.<sup>5</sup> Roentgenograms made during seizures suggest that bronchial secretion is likewise increased at this time (Fig 1). Maximal

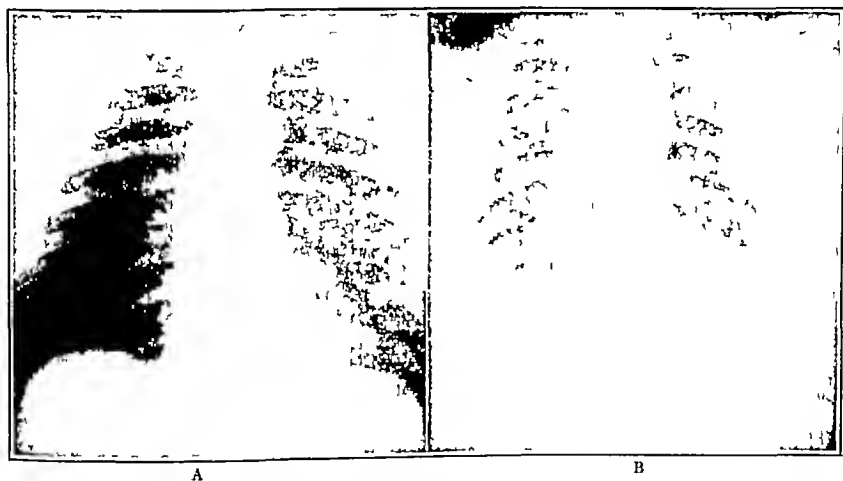


FIGURE 1 Elevation of the Diaphragm during Electrically Induced Convulsions

A demonstrates a roentgenogram of the chest immediately before electroshock and B one at the height of the tonic phase of the seizure twenty seconds after the start of the convulsion.

such seizures uniformly show an extreme degree of elevation of the diaphragm, together with some narrowing of the intercostal spaces, marked compression of the lung results (Fig 1). With the end of the convulsion the patient relaxes, and the lungs re-expand to approximately their normal size.

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inspiration, such as that occurring at the end of the seizure,<sup>2</sup> causes the aspiration of some of this material into portions of the previously compressed lung, and small bronchi may become occluded, failure of portions of the lung so blocked off to re-expand causes the atelectasis that may be found. It is probable that patchy atelectasis is more common than is usually recognized, for the condition gives rise to no symptoms and clears up in a few days. On the other hand, if infection localizes in an atelectatic area development of an abscess may

result. This complication is rare, however, having occurred only once in 200 patients given electroshock therapy during the last five years (Fig 2).

The following case is regarded as typical.

E W G, a 65-year-old unmarried typist, entered the hospital voluntarily on October 11, 1946, complaining of agitation and depression of 6 months' duration. A diagnosis of involutional melancholia was made, and physical and laboratory examinations showing no evidence of organic

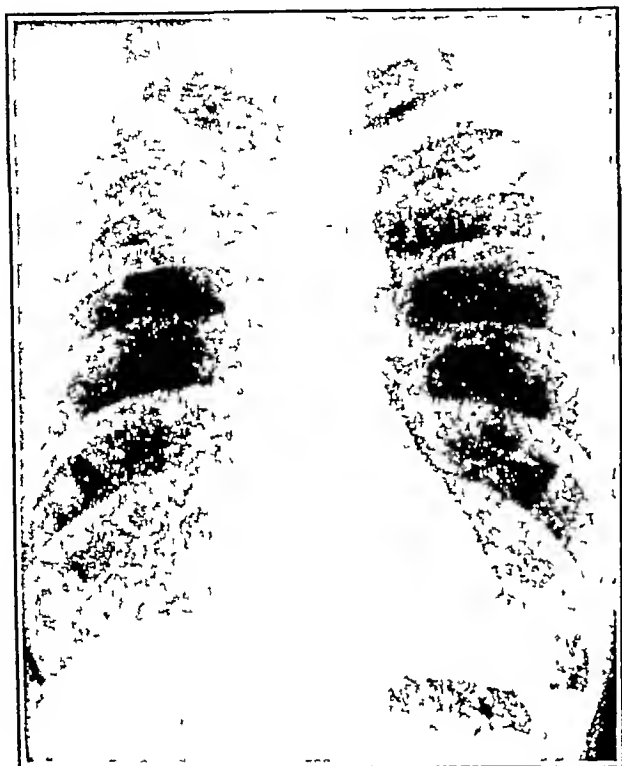


FIGURE 2 Lung Abscess, Absent before Treatment, Detected after Eighth Shock

disease, electroshock therapy was recommended. Because roentgenograms demonstrated an old compression fracture of the spine and deformity of the pelvis apparently consequent to a serious accident 19 years previously, curare (Intocostin\*) was used.

Treatments were begun on October 21 and given 3 times weekly; respiration was not depressed after the treatments. Improvement was rapid, but after the eighth treatment on November 6 the patient was noted to have fever, chilly sensations and a slight cough, and treatments were stopped. The cough was productive of a small amount of foul sputum, which the patient swallowed.

Physical examination was not remarkable except for a temperature of 101°F; roentgenograms showed an abscess of the lung. On November 14 penicillin in doses of 100,000 units given intramuscularly every 3 hours was started, and 2 days later the temperature was normal. The white-cell count varied between 9800 and 17,000 during the next few weeks. On January 4, 1947, the penicillin dosage was changed to 100,000 units in wax once daily. On January 10 the patient was considered cured clinically and by x-ray study. During the period of the pulmonary infection the depression recurred in a severe form. Another course of electroshock therapy with curare in March and April resulted in clinical cure, no pulmonary complications developed.

\*Kindly supplied by E. R. Squibb and Sons, New York City.

The reported exacerbation of latent tuberculous infection may be based on similar mechanisms and also on the tearing of brittle fibrous patches containing tuberculous organisms.

The marked changes in intrathoracic pressure that favor the occurrence of pulmonary lesions serve, on the other hand, to protect the heart during electrically induced seizures. The increase in intrathoracic pressure exerts a force on the outside of the coronary arteries that prevents an increase in difference between the internal and external pressures on the walls of these vessels and may even cause a decrease; brittle coronary arteries are thereby protected from damage. In addition the change from the normal negative intrapleural pressure to a positive pressure during the seizure retards the pas-

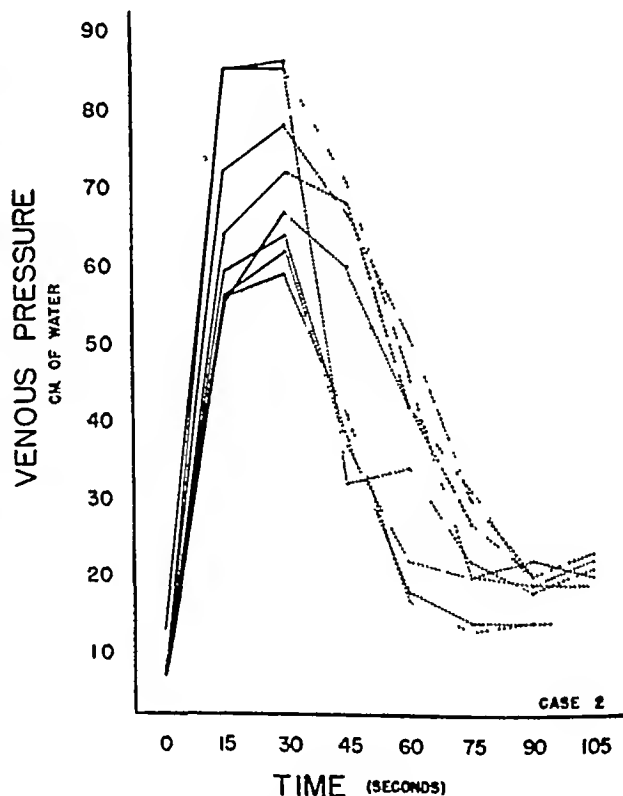


FIGURE 3 Rise in Peripheral Venous Pressure during Eight Electroshock Treatments

The solid line indicates readings during the seizure, and the dotted lines those made after the seizure.

sage of blood from the periphery into the heart, this change is reflected in the increase in peripheral venous pressure noted during electrically induced seizures<sup>2, 6</sup> (Fig 3). As a consequence of the diminished venous return of blood the heart becomes smaller than normal (Fig 1), and its work is decreased. Accordingly, it is apparent that the great increase in metabolism that occurs during the thirty or forty seconds of a convulsion is not associated

with a corresponding increase in strain upon the heart at that time. After the end of the convulsion, the cardiac work is increased, judging by the acceleration of circulation time.<sup>7</sup> However, this increase in the work of the heart is related in large part to the discharge of the accumulated oxygen debt, a process that requires many minutes, the cardiac work corresponding to the metabolic increase brought about by the convulsion is therefore not concentrated in the brief period of the seizure but is spread over a longer period and, accordingly, usually does not reach a dangerous level at any one time. Nevertheless, myocardial infarction has been reported to occur in relation to electroshock therapy, the damage probably is done shortly after rather than during the convulsion. Another factor making for a transient increase in cardiac work at this time is the return to the heart of the blood impounded in the periphery during the seizure, this release of blood occurs almost entirely during the first minute after the convulsion, for the venous pressure falls almost to normal during that time (Fig. 2).

In the following case electroshock therapy apparently aggravated the effects of an already present coronary sclerosis.

A H. L., a 52 year-old executive, became depressed in January, 1945, and because of the marked progression of his symptoms sought psychiatric advice in November of that year. The past history was not contributory except for mild hypertension. On November 1 an electrocardiogram was normal except for left axis deviation and inverted P and T waves in Lead 3. The patient was given five electroshock treatments without untoward event in November and improved markedly. However, he noted for the first time the development of squeezing precordial exertional discomfort, aggravated by exposure in cold and relieved by rest. Physical examination at that time was not remarkable except for a blood pressure of 168/110. Electrocardiograms in March, 1946, showed left axis deviation and an inverted T wave in Lead 1. Roentgenograms 3 months later revealed prominence of the left ventricle and hypertrophic changes in the spine. Electrocardiograms at that time disclosed a sinus bradycardia (the rate being 50), left axis deviation and a T wave in Lead 1. The two-step stair test, performed in a cold room, caused dyspnea and reproduced the precordial discomfort that the patient had experienced spontaneously during his normal activities. It was concluded that he had developed angina pectoris and changes in the electrocardiogram after electroshock therapy and therefore fell into the small group of patients in whom the effects of coronary sclerosis were aggravated by induced seizures.

The rush of blood from the periphery into the right auricle and great veins of the thorax during the post-convulsive period probably accounts for the cardiac arrhythmias that may occur at that time, the rhythm is normal during at least the last half of the seizure (Fig. 4). The arrhythmias are vagal in type<sup>8</sup> and are apparently consequent to reflexes activated by sudden distention of the auricles and great thoracic veins.<sup>9</sup>

It is apparent that diminution of the postconvulsive strain upon the heart would be accomplished by a decrease in the oxygen debt developed and in the amount of blood incarcerated in the periphery

during the seizure. This can be effected by the use of a suitable preparation of curare, it is possible to administer electroshock therapy to patients of advanced age and with electrocardiographic evidence of cardiac damage through the use of this drug.<sup>10</sup> It must be borne in mind that a solution of d-

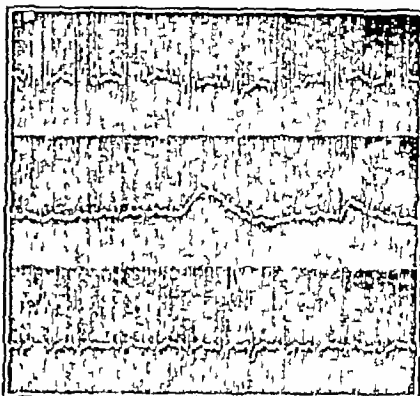


FIGURE 4 Continuous Strip of Electrocardiogram, Showing Absence of Arrhythmia during the Seizure

Normal electrocardiographic complexes are interspersed among action currents resulting from clonic muscular contractions

tubocurarine is the drug of choice, since Intocostrin may contain impurities that exaggerate to a dangerous degree the vagal impulses that influence cardiac rhythm.<sup>11</sup>

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## ANGIOCADIOGRAPHY · ITS USE IN THE DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS\*

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**ANGIOCADIOGRAPHY**—contrast visualization of the heart and great vessels—was first made a practical procedure by Robb and Steinberg<sup>1</sup> in 1938. In subsequent reports these authors have described in detail their technic of employing serial roentgenograms after the rapid intravenous injection of 70 per cent Diodrast<sup>2</sup> and, along with many others, have reported their observations in normal and pathologic cardiovascular systems. It is the purpose of this report to review briefly the clinical applications of angiocardiology, to discuss the use of this technic in a rural hospital and to report its use in the diagnosis of a case of patent ductus arteriosus.

### CLINICAL APPLICATIONS

Angiocardiology has, in general, two great advantages: it enables one to outline and differentiate the various components of the cardiac and great-vessel silhouettes, and it makes possible the differentiation of vascular and nonvascular mediastinal shadows. This technic has been employed profitably in the more academic study of normal hearts<sup>3</sup> and of various types of acquired cardiovascular disease—rheumatic,<sup>4</sup> arteriosclerotic,<sup>5</sup> hypertensive,<sup>6</sup> syphilitic<sup>6</sup> and pulmonary.<sup>6</sup> Its more practical use has been reported in cases of the superior-vena-cava syndrome,<sup>7</sup> demonstrating the site of an arteriovenous fistula of the subclavian vessels<sup>8</sup> and in differentiating aneurysms of the great vessels from other mediastinal masses.<sup>9</sup> Steinberg,<sup>10</sup> however, has mentioned 2 cases in which the dye did not fill the aneurysms sufficiently for their demonstration.

In congenital cardiovascular lesions, cases have been studied and reported of dextrocardia<sup>11</sup> and intracardiac shunts.<sup>12</sup> The greater value of angiocardiology, however, is in cases of congenital lesions amenable to surgery. By this technic it has been possible to demonstrate definitely the lesions in pulmonic stenosis<sup>13</sup> and coarctation of the aorta.<sup>14</sup> The findings in cases of patent ductus arteriosus are discussed below. Its use has not yet been reported in anomalies of the aortic arch of the type whose surgical treatment has been reported by Gross and Ware,<sup>15</sup> but again the abnormality could be exactly demonstrated. It is true that in typical cases of all four lesions the diagnosis can be made by careful clinical and roentgenographic examination. But the 2 cases of coarctation described by Grishman et al.<sup>14</sup>

were atypical ones diagnosed as rheumatic heart disease and hyperthyroidism before the lesions were demonstrated by angiocardiology. In the case of patent ductus reported below, it is believed that the diagnosis could not have been established without angiocardigraphic studies. It is also true that in cases of pulmonic stenosis and patent ductus the diagnosis can be made most accurately by cardiac catheterization,<sup>16</sup> but this is an intricate procedure and is not always available. Because of the great benefit of surgery to patients with these four lesions, it seems imperative to employ angiocardiology in atypical or suspected cases, so that no patient may be denied surgery for want of an accurate diagnosis.

In the 27 cases of patent ductus arteriosus studied by Steinberg et al.,<sup>17</sup> a distinct localized dilatation of the aorta was noted in 26. The ductus itself could not be opacified. The authors postulated that this dilatation represented either the infundibulum of the ductus, always known to be funnel shaped at its aortic end, or a traction aneurysm of the descending aorta at the base of the ductus, as originally described by Thoma. In 3 of the 12 cases in which the diagnosis was confirmed by operation, silver clips were placed on top of the ductal ligatures. Repeat angiocardigrams in these cases showed the clips to be in the exact location of the aortic dilatation. In the case in which the aortic lesion was not demonstrable, it seems possible that the clinical diagnosis might be questioned in the absence of a machinery murmur or thrill and in the presence of a peculiar axis deviation by electrocardiogram. A "slight dilatation of the descending portion of the aorta" was noted in only 1 other of the many patients examined by Steinberg et al. This patient was later found at autopsy to have an interventricular septal defect occluded by bacterial vegetations and pulmonic insufficiency secondary to an anomalous posterior pulmonic-valve leaflet (Case 3).<sup>12</sup>

### ANGIOCADIOGRAPHY IN A RURAL HOSPITAL

When this technic was employed for the first time, there were two considerations: the precautions that must be taken to make the procedure safe, and whether the method could be employed with the equipment available.

To determine what precautions should be taken, the American literature on fatalities from the administration of 35 per cent Diodrast was reviewed. Pendergrass et al.,<sup>18</sup> in their extensive review, reported 26 cases, and reports of 10 others are to be found in the literature. Of this entire group,

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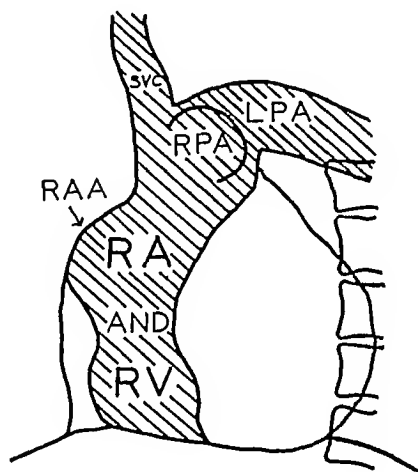
11 can only be mentioned because of insufficient data, and in 10 others Diodrast could not be identified with certainty as the agent responsible for the death. In the remaining 15 cases, death was due to a sudden anaphylactoid or shock-like response in 10<sup>18-21</sup> (Cases 1, 2, 3, 6, 7 and 10);<sup>18</sup> to acute anuria in 2, presumably caused by the effect of Diodrast on previously diseased kidneys that had blocked its rapid excretion (Cases 4 and 19)<sup>18</sup> and to a delayed type of anaphylactoid response in 3 cases, caused in

best not to attempt angiocardiology. If the history of allergy is only slightly positive, studies might be attempted after the prophylactic use of adrenalin<sup>18</sup> or perhaps Benadryl. Also, in view of the cases reported by Dolan<sup>20</sup> and Shanahan,<sup>22</sup> a history of iodide sensitivity should be sought in every case.

Of the sensitivity tests, the best at present appear to be the oral<sup>20</sup> and the ocular.<sup>23</sup> Evidence on the reliability of the skin tests is quite conflicting, but



A



B

FIGURE 1 Angiocardiogram (A) and Tracing Made from it (B) Taken in the Left Anterior Oblique Position Two and a Half Seconds after the Injection of Diodrast

SVC = superior vena cava RAA = right auricular appendage RA and RV = right atrium and ventricle RPA = right pulmonary artery, in cross section and LPA = left pulmonary artery in longitudinal section. Note the enlargement of both pulmonary arteries

2 (Cases 9 and 17)<sup>18</sup> by the delayed excretion of Diodrast by previously diseased kidneys.<sup>24</sup>

These deaths due to Diodrast therefore appear to have been caused either by an anaphylactoid response or by the effect of Diodrast on pre-existing renal disease causing delayed excretion or by a combination of the two. To eliminate patients who may have an anaphylactoid response there are two avenues of approach: a careful history of allergy, personal or familial, and sensitivity tests. Although the value of the former appears uncertain at present, it should be taken, and if strongly positive, it seems

on the basis of Taylor's<sup>25</sup> findings of a lack of correlation between the minor toxic reactions and the intracutaneous test, the test is believed to be of questionable value.

To eliminate patients who would have a delayed Diodrast excretion, the standard phenolsulfonephthalein excretion test is the most satisfactory, because of the similarity of the mode of renal excretion of the drug and Diodrast, both being filtered and secreted. Bishop's<sup>26</sup> standards of an excretion of greater than 15 per cent in fifteen minutes and 30 per cent in one hour were arbitrarily

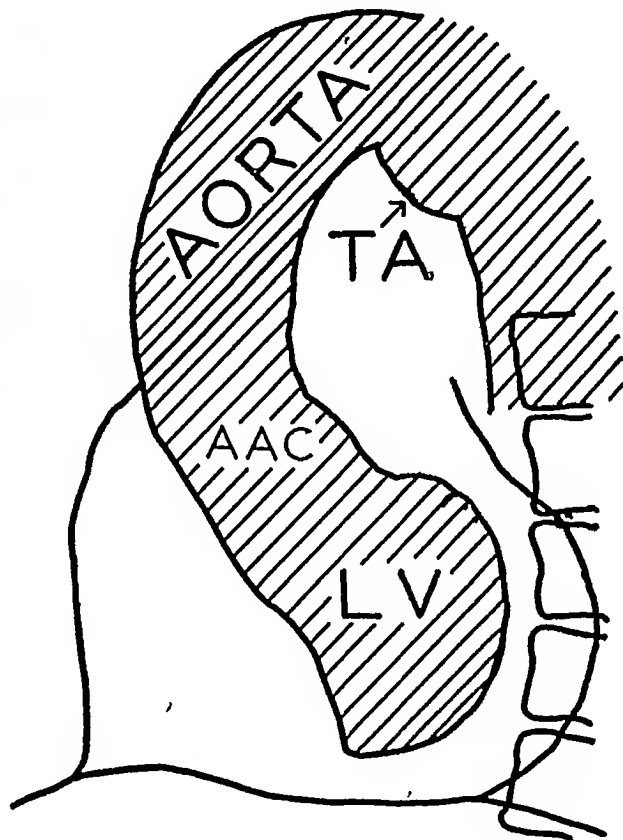
accepted. Also adopted was the suggestion, made by the Council of Pharmacy and Chemistry of the American Medical Association when the administration of 70 per cent Diodrast was approved, that the drug be withheld from patients with clinical evidence of hyperthyroidism or hepatic disease.<sup>25</sup>

It was therefore believed that the procedure would be a safe one if each patient fulfilled the following four criteria: a negative history of allergy or iodide sensitivity, negative oral and ocular Diodrast sensitivity tests, a phenolsulfonephthalein excretion of greater than 15 per cent in fifteen minutes and

springs had been removed. An assistant simply pushed a cassette into place after the exposure of the one in the machine, the latter being caught by another assistant as it was ejected. With this method six films were taken in ten seconds with but one practice run. The films were protected before and after exposure by two lead aprons suspended from a cross bar placed over the stereoscopic machine. A small table with two bookends kept the cassettes readily available for the person responsible for placing them in position. The technic employed was otherwise identical with that described by



A



B

FIGURE 2 Angiocardiogram (A) and Tracing Made from it (B), Taken in the Left Anterior Oblique Position Eleven Seconds after the Injection of Diodrast

LV = left ventricle, AAC = area of the aortic cusps, and TA = traction aneurysm of the descending aorta.

30 per cent in one hour, and no clinical evidence of hyperthyroidism or hepatic disease.

The technical problems faced were two: the injection of 50 cc of Diodrast within two seconds and the taking of serial roentgenograms in the ten seconds normally required for the passage of the dye through the heart and great vessels. The first of these was solved by the purchase of a 13-gauge transfusion needle (the only expense) and by manual filing of the bore of a 50-cc syringe until it was larger than that of the needle. The second was solved by manual passing of the cassettes through the apparatus used for taking stereoscopic films, from which the ejector lever and restraining

Robb and Steinberg,<sup>2</sup> except that an infusion was kept running through a three-way stopcock, after insertion of the needle, to ensure its patency while the circulation time was determined and positioning films were taken. It should be emphasized that anyone using this technic should be thoroughly familiar with the detailed directions outlined by Robb and Steinberg.

#### CASE REPORT\*

C L, a 30-year-old laborer, was first seen at this hospital at the age of 21 for evaluation of "valvular heart trouble." At the age of 9 a "loud heart murmur" had been heard for the first time. During the next 12 years the patient had followed

\*This case is reported through the courtesy of Drs. George M. Mackenzie and George H. Humphreys. 11

a vigorous athletic program and did not believe that his exercise tolerance had been less than that of any of the other boys. There was no history of acute rheumatic fever, scarlet fever, tonsillitis, chorea, arthritis, growing pains, precordial pain, edema or cyanosis. Physical examination at that time revealed a well developed and well nourished young man with no evidence of cyanosis, clubbing or edema. The cardiac apex was percussed 11 cm. in the fifth left interspace. No thrill was palpable. There was a regular sinus rhythm. At the base of the heart and in the area between the clavicle and the cardiac border was a continuous murmur with a systolic accentuation. This was heard with diminishing intensity down over the precordium becoming separate diastolic and systolic murmurs in the third and fourth interspaces along the left border of the sternum. The murmur was transmitted somewhat into the vessels of the neck. There was no evidence of collateral circulation and strong pulsations were palpable in the legs. Physical examination was otherwise negative. At the time the electrocardiogram was being taken, the murmur was completely absent, returning later in the afternoon as noted above. The electrocardiogram revealed slight slurring of the QRS complexes in all leads and an inverted T wave in Lead 3. There was slight left axis deviation but no other abnormalities were noted. A 6-foot film of the heart showed a somewhat rounded left cardiac border, suggesting an enlarged left ventricle. The total transverse measurement of the cardiac shadow was 140 mm. the internal thoracic diameter being 295 mm.

The patient was referred to the hospital because of pyrexia of 6 weeks duration. During the intervening years he had had no cardiac or respiratory symptoms. He was employed at heavy manual labor and was playing semiprofessional baseball. There was no history of recent dental extraction or trauma. Six weeks before admission he had suddenly experienced a shaking chill and had subsequently felt alternately hot and chilly with a persistent afternoon fever.

The patient appeared ill and had a café-au-lait complexion. There was no cyanosis, clubbing or edema. No precordial shock or thrills were palpable. The left border of the heart was percussed 12.5 cm. in the fifth left interspace. There was a regular sinus rhythm. Along the left border of the sternum at the level of the second and third interspaces was a "whirling huzzing systolic-diastolic murmur. Another observer described it as a loud rough systolic murmur. There was also a rasping, nontransmitted apical systolic murmur. The spleen was not palpable and there was no evidence of embolic phenomenon.

The temperature was 103°F. and the blood pressure was 128/66 in the arms and 144/69 in the legs. There was no fall in diastolic pressure after exercise.

A blood culture taken on the day of admission grew colonies of alpha hemolytic streptococcus in all flasks. The white cell count was 14,000, with 68 per cent neutrophils. The electrocardiogram was essentially unchanged from the record taken 9 years before. Roentgenographic and fluoroscopic examinations revealed enlargement of the left and right ventricles with no evidence of enlargement of the left auricle, pulmonary arteries and aorta. There was no hilar dance. The transverse diameter of the heart was 154 mm. Further laboratory studies revealed an ether circulation time of 5.5 seconds, with no Hitzig phenomenon, negative oral and ocular sensitivity tests to Diodrast and a phenolsulfone phthalein excretion of 28 per cent in 15 minutes and 55 per cent in 1 hour.

The patient was hospitalized for 5 1/4 weeks receiving a total of 56,000,000 units of penicillin. He was afebrile from the 4th day on, with the exception of spikes in temperature to 102°F. on the 12th and 23rd days. All blood cultures taken after the institution of penicillin therapy were negative.

### DISCUSSION

During the patient's stay in the hospital the question arose of referring him for surgery, but no definite decision was reached because the diagnosis was not clear cut. Of the ten criteria for the diagnosis of patent ductus listed by Shapiro,<sup>1</sup> this patient definitely had three, four were definitely absent, and three were questionable. He did have an enlarged heart, absence of cyanosis or clubbing

and a history of heart disease from early childhood. He did not have a thrill in the pulmonary area, an enlarged pulmonary artery, enlarged and pulsating pulmonary vessels or any stunting of growth. It was questionable if he had a machinery murmur, an increased pulse pressure and a normal electrocardiogram.

In the hope of being able to offer more conclusive evidence of the existence of a patent ductus arteriosus, angiocardigraphic studies were performed, with particular attention to the following possibilities: enlargement of the pulmonary arteries, previously not visualized by fluoroscopic examination, and the traction aneurysm of the aorta mentioned above. Prior to examination a normal subject was studied to perfect the technique and to obtain films for comparison.

The angiocardigrams of the patient in the case reported above and tracings made from them are presented in Figures 1 and 2. Both films were taken in the left anterior oblique position. The first, taken two and a half seconds after the start of the injection, shows definite enlargement of both branches of the pulmonary artery. The second film, taken eleven seconds after the start of the injection, reveals a definite fusiform dilatation of the descending aorta, just below the arch and on the side facing the pulmonary arteries. This was also visible in the films taken immediately before and after the one described above. On the basis of these two findings, the diagnosis of patent ductus arteriosus was regarded as confirmed. The patient was referred to Dr. George H. Humphreys, II, who, at operation, found and ligated a patent ductus.

### SUMMARY

The clinical applications of angiocardiology are briefly reviewed, with emphasis on its use as a diagnostic aid in atypical cases of congenital cardiovascular lesions amenable to surgery.

The use of this technique in a rural hospital is discussed, the four criteria a patient should fulfill prior to angiocardigraphic studies being listed, and the methods by which the difficulties of rapid intravenous injection and rapid serial roentgenograms were overcome being described.

An atypical case of patent ductus arteriosus is reported in which the clinical diagnosis was confirmed by angiocardigraphic studies, demonstrating enlargement of the pulmonary arteries and a traction aneurysm of the descending aorta. This diagnosis was confirmed at operation.

I am indebted to Dr. James Drorbaugh and Mr. Ivan Lawrence for assistance in performing these studies.  
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## ACUTE HEMOLYTIC ANEMIA FROM QUININE USED AS AN ABORTIFACIENT\*

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ACUTE hemolytic anemia following the administration of quinine has rarely been observed except in the presence of malaria Terplan and Javert<sup>1</sup> found 8 cases in the literature and reported a case of their own All these patients were women who had taken or been given the drug as an abortifacient All died They showed evidence of a severe degree of intravascular hemolysis and, in most cases, hemoglobinuria When measured, the nonprotein nitrogen content of the blood was found to be very high The intake of the drug was not always beyond usual therapeutic dosage as little as 0.4 gm proved fatal in 1 case Vartan and Discombe<sup>2</sup> have added another fatal case After the ingestion of 6 gm of quinine sulfate to induce abortion, the patient quickly developed icterus and black, scanty urine The terminal blood urea nitrogen was 540 mg per 100 cc Hemoglobin casts were found in the kidney at autopsy The case of a patient who recovered has been reported<sup>3</sup> She was a twenty-year-old girl who, after taking an unknown amount of quinine to cause abortion, developed jaundice, hemoglobinemia, hemoglobinuria, oliguria and uremia She recovered after resumption of renal function

The mechanism of the hemolytic process is not clear Acute intravascular hemolysis following quinine has been reported apparently only in the presence of malaria or pregnancy Ponder and

Abels<sup>4</sup> found that in rabbits quinine in very large dosage produced a slight fall in red-cell concentration and made the erythrocytes more susceptible to saponin and taurocholate hemolysis The quantity of quinine necessary was far beyond that which has produced severe hemolytic anemia in man Perhaps the quinine renders the red cell more susceptible to hemolysins that may be present during malaria and pregnancy In animal experiments Nocht and Kikuth<sup>5</sup> have shown that very small amounts of quinine may facilitate amboceptor hemolysis

We have recently observed a similar patient who made a complete recovery from severe intravascular hemolysis following quinine This case is as follows

The patient (M G H 526650), a 42-year-old mother of 8 children, entered the hospital on April 14, 1946, because of the sudden appearance of dark-red urine and profuse vaginal bleeding She described a normal menstrual history Two weeks before entry, at the time of an expected period, she began to have a spotty vaginal discharge This continued until 2 days before entry, when she felt chilly and weak and ached all over On the following morning she was surprised to find that the urine was dark red She began to have profuse vaginal bleeding and passed many clots The family noticed that the skin had become slightly yellow She continued to bleed all day and through the night, and on the morning of admission she passed a piece of tissue accompanied by many blood clots

The patient had been born near Naples and had come to the United States in 1919 The only history suggestive of malaria was that she had had "Spanish flu" as a girl in Italy during an epidemic There was no history of familial jaundice, anemia or dark urine either in the patient or in her family, many of whom were available for questioning She vehemently denied any suspicion of pregnancy or drug ingestion other than that of a few aspirin tablets taken for

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headache on the evening before entry. She had eaten no fava beans. Six pregnancies had been normal. She had had one miscarriage at 6 months following prolonged bleeding, and one threatened miscarriage. One of her children had been born prematurely.

The patient was obese, moderately icteric and acutely ill. She was dyspneic and apprehensive. The liver was slightly tender, and the edge palpable 3 cm. below the costal margin. The spleen could not be felt. There was tenderness over a small area in the left groin. There was a small amount of vaginal bleeding. The uterus was anterior, freely movable and  $1\frac{1}{2}$  times the normal size. There was moderate tenderness in both vaults.

The temperature was  $102.6^{\circ}\text{F}$ , the pulse 100 and the respirations 35. The blood pressure was 120/74.

A catheter specimen of urine was wine red and contained 103 mg. of oxyhemoglobin per 100 cc. There were no formed elements in the sediment. There was a +++ test for albumin. The serum of a freshly drawn and centrifuged specimen of blood was the same color as the urine. On analysis several days later it contained 516 mg. of methemoglobin per 100 cc. The red-cell count, which on entry was 4 100 000 fell to 2 800 000 8 hours later. The white-cell count was 50 700 with 86 per cent neutrophils. These showed toxic granulation. The red cells showed great variation in size and shape and moderate spherocytosis. Complete hemolysis of the red cells occurred when they were mixed with 0.55 per cent physiologic saline solution and partial hemolysis with 0.60 per cent, as compared with normal controls of 0.38 per cent and 0.42 per cent. The osmotic fragility had returned to normal on the 5th hospital day, with complete hemolysis at 0.38 per cent and partial hemolysis at 0.40 per cent. Tests for cold agglutinins, hemolysins and acid hemolysis and a Donath-Landsteiner test done by Dr. Charles P. Emerson, of the Thorndike Memorial Laboratory were negative. Numerous blood smears for malaria were also negative. A blood Hinton test was negative. Urine obtained on the day of admission contained 13 mg. of quinine per liter.

Jaundice disappeared by the 3rd hospital day. The non-protein nitrogen began to rise on the 2nd hospital day, and by the 5th day had reached a level of 150 mg. per 100 cc.

where it remained for 7 days. The carbon dioxide combining power of the blood fell to 18 milliequiv. per liter. Throughout that period the patient complained of headache, vomited frequently and continued to discharge necrotic tissue and blood through the vagina. This tissue proved to be placental in origin. The discharge continued until dilatation and curettage were done on the 17th hospital day. The urine output averaged about a liter per day, and the specific gravity remained close to 1.010. The nonprotein nitrogen slowly fell to normal by the 3rd hospital week. After the curettage the temperature, which had risen to  $101^{\circ}\text{F}$  daily, returned to normal. In a few days it rose again, and heavy cultures, which had previously been sterile, showed a heavy growth of *Escherichia coli*. A 4-day course of streptomycin (1 gm. daily) was followed by relapse. Persistent clearing of the urine and freedom from fever followed a 10-day course. The patient was discharged on the 44th hospital day when the red-cell count was 4 000 000.

Two weeks after admission she admitted having taken nine large capsules containing a white powder given her by a friend to interrupt a suspected pregnancy.

This report serves to call attention to the fact that quinine is an occasional cause of severe hemolytic anemia associated with jaundice and hemoglobinuria and to emphasize the danger of quinine as an abortifacient.

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## MEDICAL PROGRESS

### SYPHILIS

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#### SEROLOGIC PROBLEMS

A diagnosis of syphilis made on purely serologic grounds is to be avoided if possible, nevertheless, the necessity of relying on serologic findings is all too often inescapable. A good example of a typical situation is a survey of 82,070 consecutively examined male maritime enrollees, aged sixteen to fifty-four years.<sup>1</sup> Among this clinically healthy population, there were 783 with positive reactions to the Kahn standard serologic test for syphilis. In 47 per cent of these 783 men a diagnosis of syphilis was eventually made, weakly positive reactions proved to mean syphilis in only 20 per cent of this group, whereas strongly positive reactions indicated

syphilis in 80 per cent. Of the 783 original positive reactors, 40 per cent had but a single positive test and were proved not infected. The remaining 13 per cent had nonsyphilitic persistently false-positive reactions. This seems to be an unusually high percentage of persistently false-positive serologic tests for syphilis.

#### False-Positive Reactions

Many articles have been written regarding the false-positive reaction, and the list of diseases most commonly producing this phenomenon is well known. Nevertheless, it will again bear repetition. The highest percentage of positive reactions are found in the three syphiloid diseases, yaws, bejel and pinta. Leprosy, malaria, vaccinia and infectious mononucleosis are probably next in order of frequency.

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Technical errors are by no means rare. The so-called "biologic false-positive reactions" seem to be found with distressing frequency and are as yet not adequately explained. Many diseases have been reported from time to time as causing occasional false-positive tests for syphilis, including such conditions as upper respiratory infections, virus pneumonia, lymphogranuloma venereum, hyperpyrexia from various causes, serum treatments and assorted immunization procedures. It is also claimed that weak false-positive reactions may be caused by tuberculosis, pregnancy and cancer.<sup>43</sup> If they do occur, the incidence of false-positive reactions from these last three conditions is extremely low. False-positive reactions have also been reported in diseases associated with hyperproteinemia, such as kala-azar.<sup>44</sup> Disorders with associated hyperproteinemia do not necessarily lead to false-positive reactions, however, some may, but there are numerous others that do not. Lupus erythematosus is another disease that apparently must be added to the list. Occasional cases showing false-positive tests for syphilis have been reported from time to time and more frequently in recent years. A recent article describes a group of 3 patients, one of whom came to autopsy, 2 cases of the chronic discoid form of the disease were verified histopathologically, and the third was a case of acute disseminated lupus erythematosus that was examined post mortem.<sup>45</sup> All 3 showed false-positive reactions to syphilis at one or another time during the course of observation.

It seems apparent that nonspecific serologic tests for syphilis, considered uncommon in the past, are now becoming more numerous, particularly in precipitation and flocculation tests such as the Kahn, Kline, Eagle and Mazzini.<sup>46</sup> Moreover, it is suspected that nonspecific positive reactions occur in spinal fluids, and it is suggested that they be considered in early untreated cases in which the cell count, globulin and colloidal gold are normal and only the serologic tests positive. A thoroughly conservative attitude is obviously warranted in the serologic diagnosis of latent syphilis when no history of the disease exists.

There are some circumstances under which a false-positive blood serologic test for syphilis should be particularly suspected. In the complete absence of other evidence of the disease a disagreement in results of complement-fixation and precipitation tests should warrant suspicion, especially if only the precipitation reaction is positive. When quantitative tests are employed and provide fluctuant or low-titer reactions on repetition and if there is a decline toward negativity over a period of several weeks, the patient is probably not infected. If there has been an acute infection of any sort within thirty to sixty days prior to the suspected test, prolonged repetition is warranted, especially if a precipitation reaction alone is used. It is never desirable to depend on a single test under such cir-

cumstances, the use of several types of determinations is indicated, as well as the employment of more than one laboratory.

### *Verification Reactions*

A number of "verification" or differential tests have been devised to distinguish between syphilitic and nonsyphilitic reactions. The value of these procedures has not been established, and they are not routinely employed in laboratories for this purpose. They are applicable only to research problems and require a great deal more study before they can be recommended.

### *Quantitative Reactions*

The quantitative determination of reagin titer in a patient's serum is an entirely different procedure and has certain valuable application. Perhaps the greatest value of the quantitative test is in the follow-up study of infants born of syphilitic mothers. There may be a carry-over of the mother's reagin in the child's blood, and a steady drop in reagin titer will indicate that the child itself is not infected, the reverse (when the titer rises or remains persistently elevated) is proof of congenital syphilis. Quantitative tests may be helpful in suspected biologic false-positive reactions, a persistently high reagin titer should indicate syphilis, whereas a slowly dropping titer (without treatment) or fluctuating readings may well mean a biologic false-positive reaction. A third use for the quantitative determination is in the so-called "Wassermann-fast" or seroresistant patients. Quantitative tests may show slow changes that would not otherwise be detectable. An important but strictly experimental application of quantitative serologic tests lies in the evaluation of new antisyphilitic drugs. A most comprehensive study of differential reactions has been carried out at Duke University.<sup>47-52</sup> This work, which is reported in a series of six papers essentially comprising a monograph, represents a tremendous amount of effort. The experiments describe serologic analysis on globulin fractions with the removal of large amounts of serologically inert serum proteins. Syphilitic, presumed biologic false-positive and normal human serums were studied under external conditions in which the reaction, temperature and serum volume were controlled. The fractions thus obtained were subjected to serologic analysis, protein concentration and electrophoretic-component distribution. The known biologic false-positive human serums were seen to show a significant increase in total titer. In both syphilitic and biologic false-positive human serums the reactive antibodies were exclusively associated with serum gamma globulin. It was observed that crude protein fractions of human serums inhibited selectively the serologic activity of the globulin fraction derived from biologic false-positive human serums. The inhibitory factor may be completely

removed by absorption on cholesterol crystals. Inhibition was selectively directed toward the flocculation action of the biologic false-positive type, that of the syphilitic type being hardly affected. The inhibition phenomenon was more specific toward antigens of high chemical purity, such as cardiolipin. It was suggested that inhibition results from competition for the antigen between the antibodies of the biologic false-positive type and the inhibitor. The lack of inhibition of the syphilitic type of reaction is ascribed to a greater affinity of these antibodies for the antigen. These observations suggested a method for the preparation of antigens exclusively specific for syphilis. In mixtures of euglobulin fractions of the syphilitic and biologic false-positive types, inhibition was exclusively directed toward the latter. A preliminary survey analysis with the euglobulin-inhibition method was made on about 2000 human sera of which about 900 were of definitely established diagnostic origin. Somewhat inconclusive results obtained in a small proportion of these sera were ascribed to a combination of limiting factors, and appropriate measures have been suggested to eliminate the resulting ambiguities. Further refinements of the present method were suggested, and a final routine method is being worked out. A general summary given by the authors themselves will perhaps provide the best condensed version of this work.

The present series of papers describe the evolutionary development of a method for the serologic differentiation between true and biologic false positive reactions for syphilis. It is based on the inhibitory effect of a heat stable serum protein component on the serologic activity of euglobulin fractions of biologic false positive human sera. Agreement between serologic results and diagnostic data was observed in about 95 per cent of the total number of sera of each group.

It is obviously impractical for the practicing physician to indulge in the details of such reports as the foregoing one-hundred-and-twenty-page series of communications. The extremely brief characterization given herein however should serve to portray the tremendous amount of time and effort expended in the laboratory approach to the problem of false-positive serologic tests for syphilis.

An excellent example of the use of quantitative tests in evaluating treatment methods is reported from Bellevue Hospital.<sup>12</sup> Four different rapid-treatment programs were employed, and serologic follow-up study was carried out for extensive periods, no patient observed for less than a year was included in the report. It appeared that prolonged low-serologic titers following rapid treatment for early syphilis did not as a rule indicate failure of treatment. In late latent syphilis, sharp rises in post-treatment titers indicated the need for further treatment, so long as a gradual trend downward existed, no further treatment seemed necessary. Among patients with neurosyphilis no correlation

was found between the height of the blood reagin titer and the severity of the disease, or between the complement-fixation titers of the blood and spinal fluid.

### *Cardiolipin Antigen*

A distinct refinement in the serodiagnosis of syphilis has been the utilization of cardiolipin antigen in the various serologic tests. This is an essentially chemically pure antigen, which has been found to give more specific results.<sup>13,14</sup> In non-syphilitic cases several large series have been studied with apparently more specific results than the antigens routinely used in well established flocculation or precipitation tests. It is also held to be more sensitive than earlier techniques. The excellent results obtained with cardiolipin-lecithin antigen and the great simplicity of the technic recommended suggest that a single standard test of the blood for syphilis worthy of universal adoption can be developed. A quantitative macroprecipitation test for syphilis, employing purified cardiolipin-lecithin-cholesterol antigen has also been described.<sup>15</sup> Cardiolipin antigens used in complement-fixation and flocculation tests for syphilis may, however, produce positive reactions with blood from presumably nonsyphilitic donors in cases of malaria, infectious mononucleosis, upper respiratory infections and some supposedly nonsyphilitic patients.<sup>17</sup> Nevertheless, in a health-department laboratory employing several of the so-called "verification reactions" and quantitative serologic tests, the cardiolipin antigen technic is regarded as of the greatest dependability.<sup>18</sup>

An example of the excellence of the cardiolipin antigen is afforded by a study of the incidence of false-positive tests for syphilis in sporozoite-induced vivax malaria.<sup>19</sup> Ninety institutional volunteers for the experiment were found to develop false-positive reactions in 57 cases (63.3 per cent). The blood sera were subjected to a battery of seven serodiagnostic tests for syphilis for periods as long as eighteen months. False-positive reactions appeared on the average eight and a third days after the development of parasitemia. In the majority of subjects, the nonspecific test was transitory and of low degree. Positive reactions resulting from individual attacks of malaria persisted for intervals varying from two to ninety-eight days. Some false-positive tests persisting for longer periods were observed when successive relapses supervened before the seropositivity due to a preceding attack had subsided, a maximum of five hundred and seventeen days was encountered in 1 such case. It was noted that the blood Hinton test and a microflocculation test employing a cardiolipin antigen yielded results of high specificity in this study — a striking fact in view of their recognized high sensitivity in the serodiagnosis of syphilis.

## CLINICAL PROBLEMS

By far the largest number of publications on syphilis appearing during the last year have been concerned with therapeutic problems and mainly concern the use of penicillin. It seems advisable therefore to omit the usual subdivisions of this report relating to the clinical phases and treatment of syphilis as separate items, combining them into one main group. Therapy will thus be included with clinical problems and reactions to treatment considered in a separate portion.

Without doubt the greatest single contribution to appear in the literature on syphilis in the past year was a book by Moore.<sup>60</sup> Familiarity with this study seems essential to anyone dealing with syphilis in any of its phases. It should at least be available to the physician who may occasionally encounter this disease. The author has had an unparalleled experience in research, in the study of clinical material, and in directing the largest mass study of syphilis ever undertaken. Participating in the survey were forty-four clinics, including several military installations, numerous United States Public Health Service rapid-treatment centers and many large civilian clinics, mostly university centers. The pharmacology, toxicity and mechanism of action of penicillin are thoroughly covered. The unknown phases of the use of penicillin in syphilotherapy are clearly pointed out, and the difficulties of evaluating this new agent are adequately portrayed. To quote directly, Moore states "Several more years must elapse before reasonably final statements can be made as to its (penicillin's) use even in early syphilis, to say nothing of the various important late manifestations." Moore believes that in the present state of knowledge the most acceptable method of treatment is through the aqueous solution given intramuscularly every two to four hours, which is definitely a hospital procedure. He discusses in detail the absorption-delaying methods of administering penicillin and indicates that penicillin in oil and beeswax presents the only one that thus far has a limited current practical application. Methods of management of the various stages of syphilis are suggested. Treatment courses are outlined not only for early syphilis but also for the latent disease and late active phases such as hepatic, cardiovascular, ocular, congenital and central-nervous-system syphilis. Moore has most adequately summarized all the currently available data regarding the use of penicillin in syphilis, subjected it to critical analysis and interpreted the information with distinct clarity. It is remarkable that so much has been accomplished within so few years after the introduction of penicillin for the treatment of syphilis. Many more years—at least ten—would normally be required, but the intense co-ordination of effort applied to the study of penicillin in the treatment of syphilis during the war has enabled Moore to take seven-league steps in but a few years' time.

## Oral Penicillin

The oral administration of penicillin in the treatment of syphilis should be mentioned only to caution against its use. Experimental work with rabbits and mice infected with syphilis was not encouraging.<sup>61</sup> Limited trials in human subjects have been inconclusive.<sup>62</sup> This mode of administration will be tempting to the general practitioner under many circumstances, but should be strictly prohibited. Little enough is known regarding penicillin by parenteral administration, and oral use can as yet only be condemned.

## Penicillin in Early Syphilis

Stokes<sup>63</sup> has placed penicillin at the top of the list of agents for the treatment of syphilis and believes that it will do away with the heavy metals and arsenic altogether. He believes that arsenotherapy has already been replaced by this modality, since penicillin "acts as an arsphenamine," and that there is still a place for bismuth in the treatment of syphilis but thinks that it may eventually also be displaced. The aqueous solution of penicillin administered under hospitalization at intervals of two or three hours is advocated as the procedure of first choice. Suggested total dosages are 2,400,000 to 6,000,000 units for early syphilis, the maximum amount being used for the secondary stages of the disease. For relapsing early infections Stokes advocates double penicillin dosage given at two-hour intervals. He emphasizes the use of adequate quantities of penicillin for a sufficiently long period as initial therapy rather than the repetition of courses of penicillin.

There is available a report of a study of 8000 patients with early syphilis treated by eleven different treatment schedules at sixteen rapid-treatment centers.<sup>64</sup> The treatment programs employed penicillin in total dosages as small as 300,000 units and upwards to 2,400,000 units alone or combined with arsenoxide or bismuth, or both, with various individual doses and treatment periods, or with arsenoxide alone, or combined with bismuth. The five-day arsenical intravenous-drip method gave the most satisfactory results but was abandoned because of the high reaction rate. Penicillin alone was not satisfactory in doses of less than 2,400,000 units. Smaller amounts of penicillin, however, when combined with arsenoxide and bismuth, gave distinctly higher percentages of satisfactory results. A number of other reports indicate that the dose of 2,400,000 units of penicillin may not be sufficient for early syphilis, certainly in the secondary stage.<sup>65, 66-67</sup> Drastically higher total dosage is advocated in revised treatment schedules for the Army.<sup>68</sup> The tentative dosage for early syphilis was stated to be 6,000,000 to 8,000,000 units in seven and a half days. For relapses or reinfections the maximum amount of penicillin is to be administered with the addition of Mapharsen and bismuth. The Veterans

Administration schedule for the management of syphilis is very much like that of the Army, and it also provides a careful classification of all phases of syphilis with treatment schedules for each stage.<sup>9</sup> This is a satisfactory and practical outline, which could well be followed by anyone treating the disease. The combined use of penicillin with arsenoxide and bismuth is properly described, as well as schedules of post-treatment observation. The management of relapses is adequately covered.

Examples of the untoward results of insufficient therapy and a timely warning regarding various pitfalls that may be encountered in the penicillin therapy of syphilis appeared in these columns some months ago.<sup>10</sup> Particularly timely was the advice regarding the ill advised marriage of patients who have been treated for early syphilis with penicillin, especially those who received their therapy during the earlier days of the use of this drug, when lower dosages were employed.

A study of relapse occurring during or after penicillin therapy for syphilis is decidedly enlightening. Among 730 cases of early syphilis treated with varying dosages of penicillin, 110 relapses were observed, some occurring as late as the sixteenth month after cessation of treatment.<sup>11</sup> Second relapses occurring after retreatment with larger doses were usually seen to occur later than first relapses. Some of the original dosage schedules were soon found inadequate and omitted. In each case relapses were treated with double the original dosage, and for second relapses a total quantity as high as 9,000,000 units was administered. The gradually increasing penicillin totals quoted in the last few references indicate clearly the continued need for study of the problem of treating syphilis with penicillin. It is obvious that the optimum dosage schedules are even yet not determined for early syphilis, in which the overwhelming bulk of study has been concentrated. It should also be clear that still more careful follow-up study must be obtained in penicillin treated patients. Monthly titrated serologic tests for a period of at least a year after complete reversal to a negative test would be a desirable attainment. This is often not possible in private practice, but the physician can at least prevail upon the office patient with early syphilis to return at monthly intervals for prolonged observation with routine serologic and physical examination after penicillin therapy.

Words of caution regarding the possibility of masking early infectious syphilis with the penicillin treatment of gonorrhea continue to appear.<sup>12-14</sup> These warnings are deserving of emphasis. The quick cure of gonorrhea with this drug is indeed a blessing, but patients so treated should certainly be followed for periods of not less than six months to be sure that the delayed development of early syphilis will not go unobserved.

### *Latent Syphilis*

Less attention has been directed to this phase of the disease than any other, especially regarding penicillin therapy. Small groups of patients have been observed after penicillin treatment in varying dosage schedules. In general the response has been at least as satisfactory as that with older methods entailing routine chemotherapy. Some workers still advocate the use of iodides and bismuth or bismuth and arsenoxide. Others recommend a penicillin-arsenoxide-bismuth combination.<sup>15, 16</sup> It may be borne in mind that patients in this phase of syphilis do not require anything like the intensive therapy that is necessary for early syphilis or the late and actively destructive forms of the disease. Nevertheless, caution is indicated to avoid a therapeutic paradox, a few injections of bismuth prior to penicillin treatment will prevent a Herxheimer reaction.

### *Late Syphilis*

One of the less common varieties of visceral syphilis is involvement of the pulmonary structures. Syphilis of the lung is most difficult to diagnose and may not even be detected at autopsy. A report on 4 cases has appeared, with a classification and summary of clinical diagnostic criteria.<sup>17</sup> The disease may occur as acute syphilitic bronchial pneumonia, chronic interstitial syphilitic pneumonia, ulcerative and sclerogummatous lesions and syphilitic bronchiectasis. Roentgenographic examination is said to be the most important factor in the detection of pulmonary syphilis and in the determination of the effect of therapy. The x-ray appearance during the response to treatment is the only means by which pulmonary syphilis can be confirmed during the life of the patient.

Cardiovascular syphilis has received considerably more emphasis. In a study of untreated syphilis in the male Negro it was found that definite cardiovascular abnormality was present in about 40 per cent of subjects in the age group over sixty-five years as compared with about 10 per cent of a control series.<sup>18</sup> The treatment of cardiovascular syphilis with penicillin was approached cautiously after untoward reactions had been observed in the earlier experience with this drug. Subsequent studies indicate that significant reactions from penicillin are uncommon in cardiovascular syphilis.<sup>19</sup> In uncomplicated aortitis, doses of penicillin comparable to those used in other phases of late syphilis have been recommended.<sup>20</sup> It seems advisable nevertheless to administer bismuth therapy in preparation for penicillin in all forms of cardiovascular syphilis. In the more serious types of lesions, such as aortic regurgitation and aneurysm, it is questionable whether penicillin should be introduced.

In connection with cardiovascular syphilis, the possibility that malarial therapy used for

syphilis will produce untoward effects on the heart may be considered. A series of several thousand patients with malaria observed by a competent cardiologist during the recent war did not reveal any cardiac condition that could be specifically attributed to malaria.<sup>78</sup> Any chronic disease, especially one resulting in anemia, may produce tachycardia, premature systoles or a functional systolic murmur, and malaria is no exception. In 50 patients of this large group, who had recurrent malaria and all of whom were studied electrocardiographically, there was no finding that could be considered outside the range of normal variation or of specific import. There were no deaths from acute cardiac disease and no proved cases of chronic cardiac disease in this series, and one would thus expect none from therapy with inoculation malaria.

The treatment of gummatous hepatic syphilis with penicillin has been reported with dramatic alleviation of acute symptoms as well as objective and subjective improvement over an observation period of one and a half to two years.<sup>79</sup>

### *Syphilitic Nephrosis*

A group of 12 cases (0.3 per cent) of renal involvement were found among a large number of patients with secondary syphilis in a period of five years.<sup>80</sup> Ten were classified as nephrosis, and 2 as nephritis. Syphilitic nephrosis is characterized by pronounced albuminuria and cylindruria, with renal-function tests not significantly abnormal. In early syphilitic nephritis there is less albuminuria and more hematuria. The differential diagnosis between syphilitic and nonsyphilitic nephritis may be difficult and can be based only on response to antisyphilitic therapy. All the 12 cases responded satisfactorily to therapy, which consisted of oxophenarsine hydrochloride, oxophenarsine and fever and penicillin alone. Only 1 patient had a Herxheimer reaction. It was suggested that if markedly hemorrhagic nephritis is present, a small initial dosage should be used to avoid a Herxheimer reaction. Syphilitic nephritis should be approached with considerably more caution than the nephrotic disease.

### *Penicillin in Oil and Beeswax*

The disadvantage of penicillin therapy has been the impracticability of three-hourly injections around the clock for all except hospitalized cases. It is obvious that the country as a whole or any one section of it contains insufficient hospital facilities for proper three-hourly administration of rapidly absorbable penicillin solutions. Many attempts have been made to devise means of delaying absorption or excretion of injected penicillin to maintain effective levels in the blood. Of the numerous combinations tested, the most practical is that of calcium penicillin in beeswax and peanut oil, devised by Romansky.<sup>81</sup> The standard preparation maintained therapeutic levels for approximately twenty-four hours after a

single injection containing 300,000 units of amorphous calcium penicillin (in 4.8 per cent beeswax by weight in peanut oil) per cubic centimeter of the emulsion. This mixture is commonly referred to as "POB." The originator of POB has reported clinical observation of 4000 cases of assorted infections treated with this substance, among which 600 were more carefully studied.<sup>82</sup> The results were as satisfactory as those obtained by the multiple injections of penicillin in aqueous solution. The incidence of allergic reactions after intramuscular injection of POB was approximately 5 per cent. The preparation has shown no loss of potency at room temperature for a year's time. There is usually some soreness to pressure at the site of injection but usually no more than that following the use of aqueous penicillin. The formation of sterile foreign-body abscesses has occurred most infrequently. So far, there has been no evidence of the development of paraffinomas. Among the 600 cases studied in this report were 75 cases of early syphilis, which comprised the subject of a separate report.<sup>83</sup> The patients received 2,400,000 units during a period of eight days. Follow-up studies of penicillin blood levels showed penicillin present in the blood for a total period of fourteen days. Lesions became dark-field negative in ten to thirty-six hours, both primary and secondary lesions were healed in three to twelve days. Among 60 cases followed for a sufficient time for proper observation, there were only 2 failures. Subsequent work was undertaken with larger doses of penicillin, and a separate group of patients is being studied with the use of a crystalline penicillin suspended in oil and beeswax.

Moore's<sup>80</sup> text does not give unqualified approval of the use of POB but intimates that its usefulness may prove more satisfactory as time passes. In another communication he sounds more optimistic.<sup>84</sup> In any phase of syphilis Moore advises that the average daily adult dose should be 2 cc (600,000 units), to be given for eight to fifteen days or longer depending on the stage of the infection. For early syphilis a minimum total dose of 4,800,000 to 6,800,000 units of POB is recommended. Other observers have reported a series of 802 patients treated with 4,800,000 units of POB in eight days.<sup>85</sup> An alternate schedule of 300,000 units given twice daily showed no advantage (in percentage of failures or relapses) when compared to the 600,000 units administered in one dose. It was suggested that smaller daily doses if continued for more than eight days might prove more effective. These 802 cases were all early infectious syphilis, and the results were eminently satisfactory, the percentages of failures in the various types of early syphilis were apparently no higher than those in any other type of rapid treatment, including follow-up studies of the cerebrospinal fluid.

A number of variants and improvements on the original POB formula have appeared. There is one



clinical report of the treatment of a small group of patients with various infections with one of these newer preparations that seems entirely satisfactory.<sup>55</sup> Combinations of POB with arsenical and bismuth therapy have also been recommended. In general, the results seem to agree with those obtained by the injection of aqueous injections of penicillin, either alone or in combination with chemotherapy.<sup>57</sup> In the management of syphilis these schedules of ambulatory treatment have a tremendous advantage over the hospitalization requirement entailed by aqueous solution. The co-operation of patients is distinctly better when shorter schedules of seven to ten days are employed. This may not be entirely desirable, since there is still considerable work to be done in establishing the optimal time-dosage relation. These ambulatory schedules will be of the greatest value to practicing physicians, and doubtless many different combinations have been improvised by various persons. When such procedures become standardized and well known, the individual physician will be able to proceed with more confidence in the management of syphilis in office practice. There is one report of the POB treatment of a case of syphilitic nephrosis with a dramatic response.<sup>58</sup>

### Chemotherapy

Reports are still appearing upon the short intensive courses of arsenobismuth therapy that were under investigation at the time penicillin appeared.<sup>59</sup> Large groups of patients were studied, especially at military installations. Intensive therapeutic programs were as short as twenty days in some cases. In general the shorter and more intensive programs were found to be inherently toxic, even under expert medical supervision. In spite of relatively good response, both clinically and serologically, these reactions occurred with such severity as to make the intensive programs unjustifiable in comparison to penicillin or penicillin in addition to chemotherapy. When longer schedules were used (twenty-six weeks), the treatment was in general better tolerated, with fewer reactions and generally satisfactory results. It is obvious that great strides had been made in the improvement of older standard chemotherapy routines. The advent of penicillin has of course changed all this, but combinations of penicillin and chemotherapy, as pointed out above, give even more promise.

Newer drugs are still being studied in the field of chemotherapy.<sup>61</sup> Dichlorophenarsine hydrochloride is one that appears to be eminently satisfactory. It has rapid spirocheticidal action and promotes prompt healing of lesions. There is favorable serologic reversal and reactions for the most part are mild and infrequent. This drug gives promise of being less toxic than arsenoxide products and certainly might be employed with caution as a substitute arsenical for patients exhibiting mild reactions

to other drugs of this group, or in combination with penicillin.

(To be concluded)

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perhaps as a result of the combination of uremia and congestive heart failure I have not seen the x-ray films yet, but I am not going to change my diagnosis

DR STANLEY M WYMAN Most of the enlargement of the heart is in the left chamber The definite areas of density described in the lower lung field are probably atelectasis in both bases

DR ISAAC TAYLOR Is there any pulmonary edema?

DR WYMAN I cannot see any The question of the mass in the left kidney I cannot quite corroborate I believe that the spleen is enlarged

DR BECKMAN The kidneys were said to be big, and such enlargement is compatible with embolic nephritis, although I cannot rule out pyelonephritis

DR CASTLEMAN Have you any comment, Dr Scott?

DR THORNTON A SCOTT I agree that the patient may have had a calcific aortic valve, with superimposed bacterial endocarditis

DR SEDGWICK MEAD Were there any splenic infarcts? They are often associated with abdominal pain

DR BECKMAN And cerebral infarcts — to account for the mental confusion

#### CLINICAL DIAGNOSES

Chronic glomerulonephritis, with uremia  
Arteriosclerotic heart disease

#### DR BECKMAN'S DIAGNOSES

Subacute bacterial endocarditis, aortic valve  
Embolic nephritis  
Arteriosclerotic heart disease, with congestive failure  
Aortic stenosis  
Pulmonary edema

#### ANATOMICAL DIAGNOSES

*Subacute bacterial endocarditis, aortic valve*  
*Subacute glomerulonephritis*  
Embolic nephritis  
Renal and splenic infarcts  
Papillary adenoma of left kidney, with necrosis and hemorrhage  
Calcareous aortic stenosis

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN Autopsy confirmed the diagnosis of subacute bacterial endocarditis located on a previously calcific aortic valve There was moderate interadherence of the aortic cusps, with deposits of calcium there — not the full-blown calcareous stenosis that produces a systolic thrill but enough stenosis to produce a murmur Implanted on this old process were numerous vegetations, 3 to 6 mm in diameter, a smear of which at the time of autopsy showed streptococci

The spleen weighed over 400 gm and contained many small infarcts There were also a few emboli

to the kidneys, but the few small renal infarcts were certainly not enough to produce uremia Occasionally, in cases of subacute bacterial endocarditis, especially in those with uremia, not only embolic nephritis but also a true glomerulonephritis occurs, which is what this patient had Many of the glomeruli showed the crescent formation characteristic of glomerulonephritis There was still another renal lesion In the left kidney was a large mass, 10 cm in diameter, which at autopsy looked like renal-cell carcinoma It was very necrotic and full of purulent material, and microscopical sections showed a benign papillary renal adenoma This may have been a precursor of renal-cell carcinoma, but at autopsy there was no evidence of cancer I am almost certain that the gross hematuria that this patient had probably came from the renal adenoma rather than from the infarcts or the nephritis

There was not much edema of the lungs There was some congestion and some hemorrhage into the alveoli, which one not infrequently sees in uremia The purpura was probably a combination of the uremia and the bacterial endocarditis I am not sure that the lesions were true petechiae

DR WARREN BENNETT As I recall them, I think that they were more like purpura

DR TAYLOR That was our impression

A PHYSICIAN Was the liver normal? Was there any evidence of central congestion or cirrhosis? And how about the gastrointestinal tract?

DR CASTLEMAN The liver was normal There was only an acute erosion in the stomach I believe that the epigastric pain was probably due to the infection and to hemorrhage within the renal adenoma

DR J W ZELLER What did the parathyroid glands show?

DR CASTLEMAN They were normal

A PHYSICIAN Did the post-mortem cultures show anything?

DR CASTLEMAN No

#### CASE 34042

#### PRESENTATION OF CASE

A thirty-two-year-old housewife entered the hospital because of vaginal bleeding of ten months' duration

She had always been in good health The menses had begun at the age of ten and a half, with regular periods every twenty-eight days, lasting three to five days She was delivered uneventfully of her first child at the age of twenty-six Twenty months before admission she became pregnant for a second time Between the third and fourth months she had a two-week episode of vaginal bleeding and was confined to bed The pregnancy continued without further difficulty to a normal delivery Following delivery she had four bleeding episodes, two of which required curettage and several transfusions The tissue removed was said to be normal The

last episode began two weeks before entry and continued with the passage of large clots to the day of admission. There was no pain. No tissue was recognized among the blood clots.

Physical examination was entirely negative, except for slight pallor of the mucous membranes.

The temperature, pulse and respirations were normal, the blood pressure was 120 systolic, 76 diastolic.

Urinalysis revealed a specific gravity of 1.018, a ++ test for albumin and a 0 test for sugar. The hemoglobin was 13.2 gm. The prothrombin time and bleeding and clotting times were normal.

On the third hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR. SOMERS STURGIS: We have the history of a completely normal ovulatory function. The patient was delivered of her first child at the age of twenty-six. Twenty months before admission she became pregnant for the second time. Between the third and fourth months she had a two-week episode of vaginal bleeding and was confined to bed. The pregnancy continued without further difficulty to a normal delivery. She may have had a low implantation of the placenta or something of that sort, which was not, however, significant enough to interrupt the pregnancy since a normal delivery followed, and therefore the cause of the bleeding in the third and fourth months probably had little to do with the present chief complaint — the vaginal bleeding that started a month after delivery and ten months before entry. Following delivery — that is, in the last ten months — she had four bleeding episodes, two of which required curettage and several transfusions. That means that she had rather extensive bleeding. The tissue removed was said to be negative — negative for tumor, I assume. The last episode began two weeks before entry and continued with the passage of blood clots to the day of admission. I do not believe that the large clots had any particular significance. Recent work on the menstrual discharge shows that menstrual blood does generally clot inside the uterus and that the clot then becomes digested through enzymatic or fibrinolytic action, and for this reason, menstrual discharge does not generally clot because it has already clotted. If there are large clots it seems to be significant merely of more than usually profuse bleeding so that the clot does not stay in the uterus long enough to be digested. There was no pain. No tissue was recognized among the blood clots. Of course, fetal tissue could have been missed.

Physical examination on admission was entirely negative, except for slight pallor of the mucous membranes. I assume that to mean that examination of the pelvis was negative too. The temperature, pulse and respirations were normal. The blood pressure was normal. The urine was essentially normal, with a small amount of albumin.

Hemoglobin was 13.2 gm. The patient had had enough bleeding to have had two dilatations and curettages and several transfusions, and she had been bleeding, with large clots, for two weeks on entry. Yet she came in with a hemoglobin of 13.2 gm., which I should think indicates that she had had rather good supportive measures in the way of iron in the meantime. The prothrombin, bleeding and clotting times were normal. On the third day an operation was performed.

Essentially this is the story of a thirty-two-year-old para II with a completely normal past history and 2 normal children, the only thing of significance that I can find at all in this story is the fact that there was a great deal of bleeding originating after the second delivery. Other than this I cannot see that there is anything at all to point to any diagnosis, and one is forced to consider all the causes of uterine bleeding in a thirty-two-year-old multipara. I think that one could summarize the causes as obstetric and systemic and those due to benign and malignant tumors.

Because the bleeding originated after delivery, one might consider the obstetric possibilities first. Chorionepithelioma causing post-partum bleeding cannot be excluded. We do not know precisely when the episodes of bleeding occurred in the last ten months. In other words we cannot tell whether she had another pregnancy and a miscarriage, or perhaps a missed abortion, or whether, in spite of the fact that no tissue had been found and the dilatations and curettages were negative, a chorionepithelioma developed from such a miscarriage. I do not believe that we can get any further information on that point and must consider it as a possibility. Again, she may have had a placental polyp from another such miscarriage that could have been missed in two dilatations and curettages. She may have had puerperal sepsis causing pelvic inflammatory disease, which interfered with the function of the ovaries and the regularity of the periods, but I think that one could throw that out on the basis of the negative pelvic examination.

In considering systemic causes, anemia itself certainly was not a factor. There is no indication of hypothyroidism or other systemic disease in this history. Could this amount of bleeding have occurred from disorganization of the endocrine system following delivery? Of course, hyperplasia of the endometrium and episodes of long profuse bleeding are frequent while the patient is establishing her rhythm again following delivery. That might give a "negative" dilatation and curettage and can cause fairly profuse hemorrhage. Again, it is hard from what we are given to rule that out.

Of the benign tumors one thinks first of fibroid. If the pelvic examination was negative, there was not much enlargement of the fundus. Could the patient have had a small submucous fibroid that was involved in the two-week episode of bleeding in the second pregnancy and yet was too small to be felt?

to be felt on pelvic examination? I rather think that the chances are against that possibility, because if a submucous fibroid caused two weeks' bleeding during a pregnancy I should think that it would have been responsible for an abortion of that particular pregnancy. Certainly, the patient did not have a large fibroid or it would have been discovered at curettage. She may have had a benign polyp in the endometrium, and this again could conceivably have been missed by two dilatations and curettages, but it does not seem likely. She may also have had adenomyosis of the uterus, even though the regularity and normality of this history before the present episode seem to discount such a possibility.

Could she have had endometrial cancer? I wonder if a vaginal smear was taken. Of course, if it was negative it would tend to make one think that this was not endometrial cancer, although in our laboratory we have missed the diagnosis in about 20 per cent of the group of cancers of the fundus on vaginal smear. The patient presumably did not have cancer of the cervix, which would have been discovered on pelvic examination.

Briefly, these are some of the common causes of uterine bleeding, and the history does not leave us with very much to go on. I should like to ask if it is known whether the patient had stilbestrol at any time in the period of two weeks' bleeding when she was put to bed during the second known pregnancy. A number of patients have been given massive doses of stilbestrol for threatened miscarriage. I have heard of 2 that had hyperplasia of the endometrium and intensive flowing following normal delivery after stilbestrol treatment during pregnancy. If this patient did not have stilbestrol I am really at a loss to know what to guess as the cause in this case. I am inclined to guess that there might have been a placental polyp or a retained placental fragment due to a miscarriage of a third pregnancy following the second delivery.

DR TRACY B MALLORY: Have you any suggestion, Dr Smith?

DR JUDSON SMITH: Can you date the episodes of bleeding more accurately?

DR JOE V MEIGS: The patient bled during the last two weeks before admission.

DR SMITH: Yes, but what was the relation to her delivery?

DR MEIGS: Ten months after the delivery.

DR SMITH: It was too late for the patient to have retained products of conception. If she had a placental polyp she should have started bleeding long before, and if anybody with any competence did two dilatations and curettages on her he should have got the polyp out. It is a perfectly good history for a chorioepithelioma, and the most important fact has not come out at all and that is whether an Aschheim-Zondek test was performed and whether or not it was positive.

DR MEIGS: The test was not done.

DR SMITH: There have been patients with negative Aschheim-Zondek tests and negative curettage that turned out to have chorioepithelioma. But that is a little bit fantastic.

#### CLINICAL DIAGNOSES

Hyperplastic endometrium

Anovulatory menstruation

#### DR STURGIS'S DIAGNOSIS

Placental polyp

#### ANATOMICAL DIAGNOSIS

*Normal uterus*

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Dr Meigs, do you want to tell us what you found?

DR MEIGS: This patient just bled, that is all. She kept bleeding even though there was absolutely nothing wrong that we could make out. Since she had cervical lacerations and a moderate amount of prolapse the best way to treat her was to do a reconstructive procedure with removal of the uterus.

DR MALLORY: The uterus was perfectly normal. The endometrium was in a proliferative phase. It was not even significantly hyperplastic, so that we have no anatomic explanation of the bleeding.

DR SMITH: I have seen 2 or 3 cases of persistent bleeding after a pregnancy in which no cause was ever found and the only cure was a hysterectomy.

DR MEIGS: The patient bled herself down so that she was miserable, and then somebody curetted her, and then the same thing started over again. She had been bleeding for two weeks and was much upset about it, and operation was the only way to stop the bleeding. I think that she was the kind of patient one sometimes wants to give radium to.

If we read over the case histories on gynecologic rounds in the hospital there is no question that there are many patients who come in with unexplained bleeding, why they bleed, I do not know. Perhaps women ought not to menstruate so often as they do. As soon as a woman comes of age and delivers an egg she is biologically supposed to become pregnant like any animal, and she is supposed to keep pregnant and nurse, and keep pregnant and nurse, until she either cannot have any more children physiologically or she dies. I think that we are bound to have, and that we do have a great many cases of unexplained bleeding. Perhaps we shall never know the answer.

DR MALLORY: Our policy in these exercises is ordinarily to discuss cases in which an anatomic specimen establishes the diagnosis beyond reasonable doubt. It is well worth while occasionally to remind ourselves that the most careful histologic examination may reveal nothing in the face of severe functional disorders.

# The New England Journal of Medicine

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

## POSTGRADUATE LECTURE COURSE — 1948

THE third annual postgraduate lecture course in general medicine, presented by the Massachusetts Medical Society and arranged by the Committee on Postgraduate Education, will be held again this year in Sanders Theater, Harvard University, Cambridge. Beginning on Monday, March 8, at 6:00 p.m., the course will run regularly on Mondays from 6:00 to 9:00 and on Wednesdays from 3:00 to 6:00 through May 5. The course is free to all physicians residing in New England, membership in the Massachusetts Medical Society is not necessary for attendance.

Special features presented for the first time this year will be sessions on cancer diagnosis and treat-

ment — the first two of the course — presided over by Dr. Charles C. Lund and Dr. Ira T. Nathanson, a session on April 26 on convulsive seizures, presented by Dr. Wilder Penfield, of Montreal, and Dr. H. Houston Merritt, of New York City, under the joint chairmanship of Dr. William G. Lennox and Dr. Maxwell E. Macdonald, and a clinical, roentgenologic and pathological session to be presided over by Dr. Merrill C. Sosman on April 12. An outline of the program appears on page xi in this issue of the *Journal*.

This lecture course, an outgrowth of the work of the Committee on Postwar Planning, has met with a universal response. In 1947 over 1200 physicians registered for forty-eight hours of instruction, as President O'Hara pointed out in his address to the Society in May, 1947, the course was the equivalent in hours of instruction of a complete college education for over twenty students. Dr. W. Richard Ohler, chairman of the Committee on Postgraduate Education, was referred to as "president of Sanders College," and Dr. Lewis M. Hurxthal, chairman of the subcommittee in charge of the course, as "dean."

Even greater success is expected for the coming course. As before, return postal cards will be sent to all registered physicians in Massachusetts. Those who wish to register immediately for the course should do so by writing to the Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston.

## MEDICAL CARE FOR VETERANS

IN THE October 11 issue of the *Journal of the American Medical Association* appears a most encouraging report from the National Medical Advisory Board of the American Legion. This board submitted several recommendations, which were adopted by the National Convention of the American Legion at its meeting in New York in August, 1947. In general, it appears that the American Legion is enthusiastic about the improved care to veterans, particularly in hospitals that are now affiliated with medical schools through the deans' committees. The Legion went on record as favoring medical research in all its

phases, and approved of the residency program. It even recommended the extension of this residency program to include outpatient clinics, in the expressed belief that this approach would assure the veteran the best medical care possible.

Those who are familiar with the problem consider the extension of the resident teaching service to the outpatient clinics a vital necessity, and it is encouraging to have a group of lay people recommend the adoption of this plan. In addition, the Legion recommends that an intern service in the hospitals where it is appropriate be adopted, and it is in favor of introducing clinical clerkships in the clinical hospitals, to be under the direction of the resident staff members and the supervision of the deans' committees.

This is another step forward. If these recommendations were adopted, there would be available in Greater Boston a vast amount of material that is not now utilized for teaching, and the use of interns and clinical clerks would do much to lighten the routine of the residents now in training. This would result in even better use of these residents for the actual care of the patient. The Legion concluded its recommendations as follows: "It is recommended to the Congress of the United States that when economy is to be practiced in the nation, it should not be at the expense of the health of the veterans who saved the nation."

The policies of General Bradley and General Hawley established good principles for the care of the disabled veteran and, in the past two years, have produced extraordinarily gratifying results, particularly as they apply to the affiliated hospitals with their resident training programs. It is even more gratifying to learn that these policies and their results have so impressed the committee of the American Legion that the Legion has gone on record as stated above. This is no time to be complacent, however. The good results of these policies will continue only so long as they are in charge of public-spirited and unselfish personnel. The care of war casualties must be maintained on a high level and with the minimum amount of interference from those whose policies might be unduly swayed by political expediency.

## A D A FORECAST

The American Diabetes Association on January 1, 1948, put into publication a new, small journal for the general public. The *A D A Forecast* "is designed to extend the doctor's influence, to save his time and to aid in the control of diabetes and the detection of cases yet undiagnosed."

The annual subscription rate for residents of the United States and Canada is \$2.00 for twelve issues. Subscription blanks may be obtained from doctors and druggists and from the American Diabetes Association, Inc., 1 Nevins Street, Brooklyn 17, New York.

Even with the probability that too much printed matter, in the aggregate, sees the light of day, there is always room for more that conveys a message. This is the case with the *A D A Forecast*, which we welcome for the value it will have to diabetic patients the country over.

## MASSACHUSETTS MEDICAL SOCIETY DEATHS

**BRIGHT** — James C. Bright, M.D., of Fall River, died on November 12. He was in his seventy-fifth year.

Dr. Bright received his degree from Jefferson Medical College of Philadelphia in 1907.

His widow survives.

**COPELAND** — Elmer H. Copeland, M.D., of Northampton, died on December 25. He was in his eighty-seventh year.

Dr. Copeland received his degree from New York Homeopathic Medical College and Flower Hospital in 1893. He was a member of the staff of the Cooley Dickinson Hospital and was formerly a censor, commissioner of trials and vice-president of the Hampshire District Medical Society.

Two daughters, two sons and two grandchildren survive.

**KING** — George C. King, M.D., of Fall River, died on December 21. He was in his sixty-second year.

Dr. King received his degree from Tufts College Medical School in 1909. He was a member of the American Academy of Pediatrics and the New England Pediatric Society and was a fellow of the American Medical Association. He was a member of the Board of Trustees, chief pediatrician and member of the staff of the Truesdale Hospital, as well as a former president of the Fall River Anti-Tuberculosis Society.

His widow, a daughter, three sons, his mother, three brothers, two sisters and two grandchildren survive.

**LORD** — William J. Lord, M.D., of Great Barrington, died on December 16. He was in his forty-first year.

Dr. Lord received his degree from Albany Medical College in 1939. He was an officer in the United States Army Medical Corps in World War II.

His widow, his mother, a daughter and two sons survive.

**REESE** — John A. Reese, M.D., of Attleboro, died on December 10. He was in his sixty-third year.

Dr. Reese received his degree from Tufts College Medical School in 1908. He was chief surgeon of Sturdy Memorial Hospital and was a fellow of the American College of Surgeons and American Medical Association.

His widow, a son and a daughter survive.

## MISCELLANY

### FIFTH ANNUAL TROPICAL MEDICINE AWARD

The fifth annual award of the Richard P. Strong Medal for outstanding service in the field of tropical medicine was made to Dr. Neil P. Macphail, veteran surgeon and sanitarian of the United Fruit Company at Quirigua, Guatemala. It was recently announced. The award was presented at the annual dinner of the American Foundation for Tropical Medicine at the Waldorf Astoria in New York City on January 8.

Dr. Macphail has been active in tropical medicine in Central America since 1907 when he accepted a position as quarantine doctor for the plague ridden port of Belize, British Honduras. In the following year he became medical superintendent of the United Fruit Company's East Coast division of Guatemala, a position he still holds. During the past forty years his efforts in combating yellow fever, cholera, endemic malaria, dysentery, snake bite, night blindness and other tropical maladies have earned for him the nickname "El Amado Medico" (the beloved doctor).

Other recipients of the medal, in addition to Dr. Strong have been Rear Admiral Edward R. Stitt, United States Navy, internationally noted author of basic texts on tropical medicine; Brigadier General George R. Callender, United States Army, a leader on tropical medical administration during World War II; and Dr. Neil H. Fairley, Australian authority on tropical diseases.

### AGING OF TWINS

Columbia University has been awarded a grant of \$31,500 by the Rockefeller Foundation for the investigation of the interaction of hereditary and environmental factors in relation to problems of aging. The grant is a renewal of an original gift made by the Foundation in 1945 to the New York State Psychiatric Institute, a part of the Columbia Presbyterian Medical Center.

To the study the health status and activities of New York State twins over sixty years of age who reside in institutions for the aged are being compared with those of twins outside institutions.

## CORRESPONDENCE

### ANOTHER DISTINGUISHED WOMAN PHYSICIAN

To the Editor: I was very much interested in reading the editorial Madame President in the November 13 issue of the *Journal*.

May I suggest that in addition to laying claim with pride and distinction to being the home of the first woman president of the American Public Health Association, Dr. Martha May Eliot, your great medical center can also lay claim with "pride and distinction" to being the home of the first woman president of the American Gastroenterological Association. Dr. Sara M. Jordan, chief of the Division of Gastroenterology of the Lahey Clinic.

Dr. Jordan was for many years the only woman member of the American Gastroenterological Association and two years ago was elected its first woman president. She furthermore enjoys the distinction of being one of the nation's outstanding woman clinicians, being especially well recognized for her very creditable work in the field of gastroenterology.

RUSSELL S. BOLES, M.D.

Rittenhouse-Plaza, Philadelphia

### CLINIC CONSULTATION SERVICE AT

### JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

To the Editor: We should like to call your attention to the fact that, owing to enlarged facilities, we can now take ambulatory diagnostic patients through our Clinic Consultation Service with a minimum of waiting. On our present appointment schedule a patient's first visit can be planned within a week.

This service is similar in every way to the diagnostic service rendered to patients admitted to the hospital except that the

patients are ambulatory and no benefits are paid for such care under the existing Massachusetts Blue Cross.

Because of the pressure for hospital beds we are anxious to care for patients on an ambulatory basis, and we should appreciate your co-operation in directing as many patients as possible to the ambulatory Clinic Consultation Service rather than having them admitted to the hospital.

Appointments for the Clinic Consultation Service can be made by calling HA 6-5650 Extension 377.

RICHARD T. VIOUERS, Administrator

Joseph H. Pratt Diagnostic Hospital  
30 Bennet Street  
Boston

## BOOK REVIEWS

*R K G Rheocardiography. A method of circulation investigation and diagnosis of circulatory motion.* From the Nerve-Clinic, the Physiological Institute, and the Pharmacological Institute of the University of Vienna. By W. Holzer, K. Polzer, and A. Marko. Translated by Mrs. Emma M. Kreidl. 8, paper 43 pp. with 44 illustrations. Vienna: Wilhelm Mandrich, 1946.

This small booklet, which was published in Vienna in 1945 and translated into crude English by Emma Kreidl in 1946 was issued as the first volume of a collection of books on the application of natural science in physics to medical research.

The rheocardiograph is a device for measuring electrical impedance. When it is connected to the right and left arms of a subject by means of electrocardiographic electrodes, a rhythmic motion that corresponds to the heart beat is registered. The authors claim that this rhythmic registration represents the action of the left ventricle. The rheocardiograms recorded in this booklet closely resemble arterial pulse tracings but lack their details.

Electrical-impedance measurement of the body is not new. Hubert Mann (*Proc. Soc. Exper. Biol. & Med.* 36:670, 1937) states:

When the electrical conductivity of any part of the body is measured by means of an alternating current bridge it is found that this conductivity shows a rhythmic variation synchronous with the pulse. Neybour (*Medical Physics*, Glaser) describes the method with a complete bibliography and refers to the curve as an electrical plethysmogram.

Electrocardiographic records of the left ventricle are dissimilar to the rheocardiogram. An electrocardiogram of the aorta shows a greater similarity to the rheocardiogram as does any large arteriogram.

It is worth while to explore the application of all kinds of new techniques to medical science. Little of value has been shown by such application of rheocardiography as that presented in this book, but whether something more useful will eventually be demonstrated remains for the future to reveal.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*State Central Case Record Systems and Local Case Registers for Tuberculosis*, 12<sup>th</sup>, cloth, 88 pp. Washington, D. C.: Federal Security Agency, United States Public Health Service, Tuberculosis Control Division, Washington, D. C., 1947.

To be fully effective tuberculosis-control programs must be supported by accurate and complete record systems. This manual has been prepared for the purpose of assisting in establishing uniform state record systems and co-ordinating them with local case registers. The primary objectives of the state system are program management, supervision and evaluation. Local case registers are necessary for case

management and evaluation and definition of local problems. The material presented in this manual is based on extensive field studies, particularly in the states of Kansas and Oregon. The text is divided into a number of sections devoted to the various details of equipping, setting-up and managing state record systems and local registers. The binding is done in the loose-leaf style, not adapted to rugged use. The printing and chart work are excellent. The manual should prove useful to public-health workers interested in tuberculosis work.

*Medical Addenda. Related essays on medicine and the changing order.* Studies of the New York Academy of Medicine Committee on Medicine and the Changing Order. 8°, cloth, 156 pp. New York: The Commonwealth Fund, 1947. \$1.75.

This supplementary volume contains six essays by eminent authorities on special problems related to the general studies of the committee. Dr. James A. Miller writes on "The doctor himself," stressing the fact that the quality of medical service depends primarily on the physician himself. The late Dr. Louis Hamman discusses psychosomatic medicine. The remaining papers are by Miss Mary A. Cannon and Miss Harriett M. Bartlett on medical social work, Winifred W. Arrington on psychiatric social work, Dr. Howard A. Rusk on rehabilitation and convalescence and Dr. Ernst P. Boas on chronic diseases. The publication is excellent in all ways, and the volume should be in all medical and social libraries.

*Health and Rehabilitation through Chest Training.* By Samuel Delano, M.D. 8°, cloth, 142 pp., illustrated. New York: Williams-Frederick Press, 1947. \$2.50.

In this small volume Dr. Delano explains his special system of chest training. The text is divided into three parts, one, physiology of the chest, lungs, diaphragm and breathing, two, special system of chest movements, with directions for their use, three, results of chest training in pathologic conditions. The text is well printed, with a good type on good paper and is well illustrated with good photographs and x-ray plates of the chest. The book should be in all collections on physical medicine.

## NOTICES

### MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The annual meeting of the Massachusetts Public Health Association will be held on Thursday, January 29, at the Massachusetts Institute of Technology. There will be section meetings at 3:30 p.m. A dinner meeting will be held at 6:00 p.m. in the Campus Room, Massachusetts Institute of Technology Graduate House, the charge will be \$1.75, including tax and tip (reservations must be made by January 26 with Mrs. Elizabeth Caso, Harvard School of Public Health, 55 Shattuck Street, Boston). At the evening meeting at 7:00 p.m. C. Mayhew Derryberry, Ph.D., chief, Office of Health Education, United States Public Health Service, will speak on the subject "Health Education — a Catalyst."

### NATIONAL CONFERENCE ON MEDICAL SERVICE

The National Conference on Medical Service will be held at the Palmer House, Chicago, on Sunday, February 8, the 1948 session being opened by the president of the Conference, Dr. Creighton Barker, of New Haven, Connecticut, at 9:30 a.m. "The Practice of Medicine by Hospitals, Health Departments and Medical Schools" will be discussed by Everett W. Jones, general manager of the *Modern Hospital*, Chicago, and Dr. Lowell S. Goin, of Los Angeles. Dr. L. F. Foster, of Bay City, Michigan, will speak on the topic "Medical Public Relations Begins in the Doctor's Office," and Dr. Thomas P. Murdock, of Meriden, Connecticut, and Janet Geister, of Chicago, on "Nursing Problems in America."

The afternoon will be devoted to panel presentations of the subjects, general practice and specialty boards, to be participated in by Dr. Wingate M. Johnson, of Winston-Salem, North Carolina, Dr. C. F. Wilkinson, of Ann Arbor, Michigan, Dr. Leroy E. Parkins, of Boston, Dr. Paul Titus, of Pittsburgh, and Dr. C. N. H. Long, of New Haven, Connecticut.

### AMERICAN HOSPITAL ASSOCIATION

The American Hospital Association will hold the first in the 1948 series of institutes on hospital-personnel relations at the Henry Grady Hotel, Atlanta, Georgia, on February 23-25. This institute is planned to give assistance and to stimulate planning for improved employee relations, not to train personnel officers. Administrators, assistant administrators and personnel officers will be helped to develop and maintain efficient work forces.

Limited to an enrollment of 75, the institute is planned to utilize the three days fully, and those attending are urged to plan longer stays in Atlanta if they desire to visit local hospital or scenic spots.

### NEW YORK TUBERCULOSIS AND HEALTH ASSOCIATION

The Annual Conference of the New York Tuberculosis and Health Association will be held on Tuesday, March 9, at the Hotel Pennsylvania, New York City. Authorities on tuberculosis, social hygiene and health education will present papers at morning and afternoon sessions. The luncheon meeting will feature an outstanding speaker.

The Tuberculosis Sanatorium Conference of Metropolitan New York will meet simultaneously and will elect officers for the coming year.

### FIFTIETH ANNIVERSARY OF CORNELL UNIVERSITY MEDICAL COLLEGE

Cornell University Medical College celebrates its fiftieth anniversary this year. The Alumni Day, which will be held on March 11 at the College, is an event of special significance to all graduates. The program will include registration in the morning, with luncheon at the Nurses Residence, to be followed by a business meeting and a schedule of rounds and conferences in all departments. Dinner will be served at the Roosevelt Hotel, and dancing will conclude the day.

### INTERNATIONAL COLLEGE OF SURGEONS

The sixth international assembly of the International College of Surgeons will be held in Rome, Italy, at the invitation of the Italian Government, during the week of May 16-23, under the presidency of Professors Raffaele Bastianelli and Raffaele Paolucci, of Rome, and Mario Dogliotti, of Turin. The secretary of the assembly is Professor Giuseppe Bendandi, of Rome. Detailed information may be obtained from Dr. Max Thorek, general secretary, 850 Irving Park Road, Chicago 13. For travel information, application should be made to the All Nations Travel Bureau, 38 S. Dearborn Street, Chicago, the official travel representatives for this assembly.

### NEUROPSYCHIATRIC RESIDENCY AT VETERANS ADMINISTRATION HOSPITAL, LYONS, NEW JERSEY

Openings are available in neuropsychiatric residency at the Veterans Administration Hospital, Lyons, New Jersey.

The program consists of one, two or three years of training with intensive postgraduate teaching in clinical neurology and psychiatry, psychopathology, clinical psychology and related sciences and in neuroanatomy, neurophysiology, neuropathology and neuroendocrinology, as well as experience in female and child outpatient psychiatry and in-hospital training for female patients and feeble-minded children and juvenile delinquents.

The type of instruction, supervision and training is carried out in accordance with the requirements of the American Board of Psychiatry and Neurology.

The residency has been approved by the Council on Medical Education and Hospitals, American Medical Association, and by the American Board of Psychiatry and Neurology.

(Notices concluded on page xvi)

## NOTICES (Concluded from page 136)

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 29

- FRIDAY, JANUARY 30**  
 \*10:00-11:00 a.m. The Clinical Significance of Various Types of Peripheral Nautitis. Dr. D. Denny Brown, Joseph H. Pratt Diagnostic Hospital  
 \*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.
- MONDAY, FEBRUARY 2**  
 \*12:15-1:15 p.m. Clinicopathological Conference Peter Bent Brigham Hospital
- TUESDAY, FEBRUARY 3**  
 \*12:00 p.m. V-Ray Conference Margaret Jewett Hall Mt. Auburn Hospital Cambridge  
 \*12:15-1:15 p.m. Clinicorootenological Conference Peter Bent Brigham Hospital
- WEDNESDAY, FEBRUARY 4**  
 \*12:00 p.m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
 \*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater Children's Hospital.

\*Open to the medical profession

- JANUARY-APRIL.** Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.
- JANUARY 23-27 AND 30.** Lowell Lectures on the Hospital in Contemporary Life. Page 106, issue of January 15.
- JANUARY 26.** New England Heart Association. Page 72, issue of January 8.
- JANUARY 26 AND 27.** American College of Surgeons. Anale Hotel, Atlanta, Georgia. Page 390, issue of December 11.
- JANUARY 27.** Norfolk District Medical Society. Page 72, issue of January 8.
- JANUARY 29.** Massachusetts Public Health Association. Page 136.
- JANUARY 30 AND 31.** American College of Surgeons. Oklahoma Billmore Hotel, Oklahoma City. Page 390, issue of December 11.
- JANUARY 30 AND 31.** Conference on Normal and Pathologic Physiology of Pregnancy. Page 1004, issue of December 25.
- FEBRUARY 6.** American Board of Obstetrics and Gynecology. Page 36, issue of January 1.
- FEBRUARY 8.** National Conference on Medical Service. Page 136.
- FEBRUARY 12.** Slippling of Upper Femoral Epiphysis. Dr. John A. Kelly. Pentecost Association of Physicians. 8:30 p.m. Haverhill.
- FEBRUARY 21-25.** American Hospital Association. Page 136.
- FEBRUARY 23-25.** Postgraduate Assembly in Endocrinology. Page 36, issue of January 1.
- MARCH 9.** New York Tuberculosis and Health Association. Page 136.
- MARCH 11.** Fifteenth Anniversary of Cornell University Medical College. Page 136.
- MARCH 28-APRIL 4.** American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler Boston.
- MARCH 19-23.** American College of Physicians. Page 216, issue of July 31.
- MAY 6-8.** American Association for the Study of Gout. Page 216, issue of July 31.
- MAY 16-23.** International College of Surgeons. Hotel Statler Boston.
- MAY 20.** American Urological Association. Hotel Statler Boston.
- MAY 18-22.** American Association on Mental Deficiency. Copley Plaza Hotel, Boston.
- MAY 25-27.** Massachusetts Medical Society. Annual Meeting. Hotel Statler Boston.
- JULY 12-17.** First International Polymyositis Conference. Page 36, issue of January 1.

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

- MARCH 9**  
 \*11:00 a.m. Annual Meeting. Hotel Weldon.  
 All other meetings will be held at the Franklin County Hospital.

## MIDDLESEX EAST

- MARCH 24**  
 \*11:00 a.m. Annual Meeting.  
 All meetings will be held at the Bear Hill Golf Club.

## NORFOLK

- JANUARY 27.** Round Table Discussions: Bleeding from the alimentary tract.  
**FEBRUARY 24.** Obstetric and Gynecologic Night.  
**MARCH 23.** Harvard Night.

## PLYMOUTH

- FEBRUARY 19.** Toll House, Whitman.  
**MARCH 18.** Goddard Hospital, Brockton.  
**APRIL 15.** State Farm, Bridgewater.  
**MAY 20.** Lakerville Sanatorium, Lakerville.

## WORCESTER

- FEBRUARY 11.** Worcester State Hospital.  
**MARCH 10.** Memorial Hospital.  
**APRIL 14.** Habersham Hospital.  
**MAY 12.** Annual Meeting.

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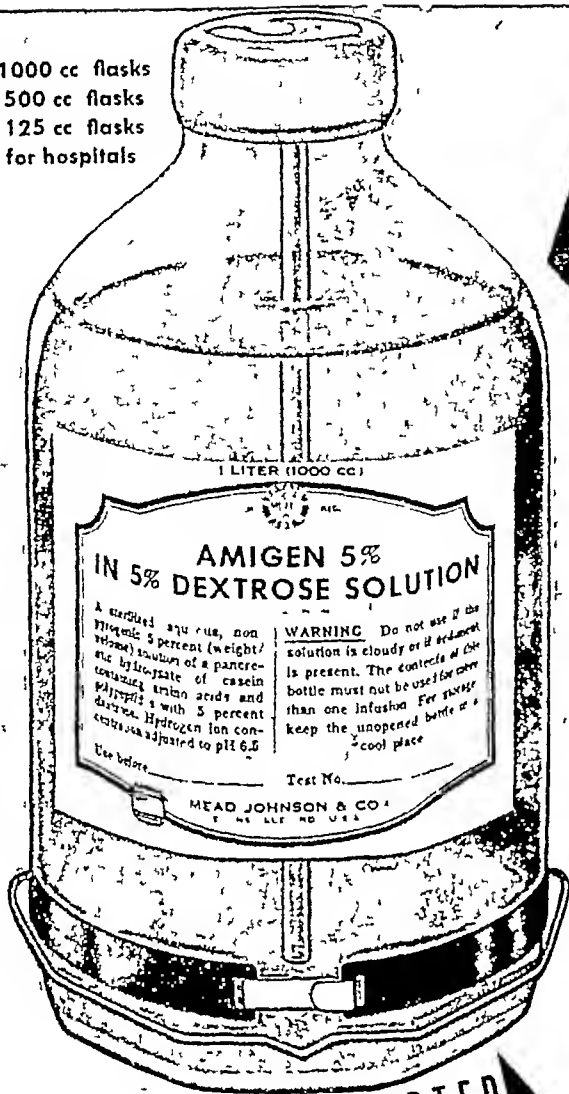
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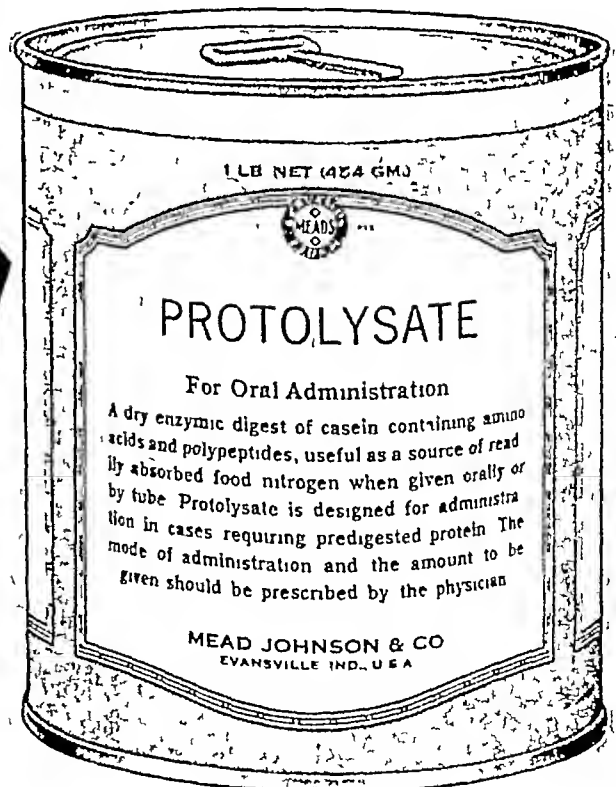
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Number 5

## THE CONTROL OF ACUTE RESPIRATORY INFECTIONS IN INDUSTRY\*

GEORGE F. WILKINS, MD†

BOSTON

THE acute respiratory diseases to be discussed today embrace acute infections known as the common cold, pharyngitis, tonsillitis, laryngitis, bronchitis, grippe and influenza. Their relative incidence and severity are essentially the same in the industrial population and in the general population as a whole. They are not occupational diseases. However, in that they are responsible for more illness and loss of production effort than any other single cause, they continue to pose a major problem for industry. Since the majority of these infections are relatively mild in character, result in only a short period of incapacitation and usually do not require medical attention, statistics regarding this class of diseases are quite unreliable. However, it has been estimated that in the United States each employed male loses an average of three days and each employed female an average of four to five days from work annually because of acute respiratory disease.<sup>1</sup> Since there are about 32,000,000 men and 12,000,000 women employed in industry the importance of this problem is evident.<sup>2</sup>

The relative significance of respiratory illness as a factor in absence from work (in excess of seven consecutive days) at the New England Telephone and Telegraph Company is demonstrated by the following data for the five-year period from 1936 to 1940, inclusive, upper respiratory infections were responsible for 37.4 per cent of all sickness absences among men and for 45.1 per cent among women. For the year 1941 alone, respiratory illnesses accounted for more than 50 per cent of all illnesses in excess of seven days in both sexes.

The causative agents in the majority of acute respiratory infections are not known. Presumably they are of viral origin in most cases, but to date only the viruses of influenza A and B have been definitely identified.<sup>3,4</sup> During the winter of 1943-1944, the respiratory illnesses occurring among new recruits at Ft. Bragg during two respiratory epi-

demics were studied. In the first wave, from November 28 to December 24, 80 to 90 per cent of all patients admitted to hospitals for respiratory disease showed increased titers to influenza A. In the second wave, occurring in late December and early January, less than 5 per cent showed increased titers against influenza A. A search was also made for hemolytic-streptococcus infection, and only a few sporadic cases were found. In this second wave more than 90 per cent of the cases were classified as respiratory diseases of unknown etiology, referred to by the Commission on Acute Respiratory Diseases as "ARD." Similar findings have been reported in other studies. Because the viral agent or agents have not yet been identified, prevention of these infections by any procedures of immunization still lies in the future.

Viruses in general have a definite biologic characteristic in which they differ from the pathogenic bacteria. They are obligate intracellular parasites—that is, they require living cells in which to multiply.<sup>5,6</sup> Because of this intracellular existence, they cannot be reached by the ordinary chemotherapeutic or other forms of medication taken up by the blood. It is for this reason that specific therapy of viral infections is for the most part ineffective. There are some exceptions, such as the favorable results obtained with the sulfonamides in trachoma and lymphogranuloma inguinale, and with penicillin in experimental psittacosis.<sup>7</sup> Although the organisms in these conditions are large rickettsia-like viruses, they are nevertheless intracellular. The fact that viruses are obligate parasites also postulates the existence of reservoirs of these agents, otherwise, the diseases they produce would soon pass out of existence. These reservoirs apparently exist in the nasopharynxes of endemic and sporadic cases and perhaps perennially in healthy carriers.<sup>8,9</sup> The principal methods by which these infectious agents are transmitted from one person to another are considered to be four in number as follows:<sup>10</sup> contact—transmission directly as in kissing or indirectly by contaminated hands, instruments or other material

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objects, droplets\* — transmission directly by projection onto the conjunctivas or skin as in coughing and sneezing, droplet nuclei — transmission indirectly by inhalation of the small residues that result from evaporation of droplets and may remain suspended in the air of enclosed spaces for indefinite periods, and dust — transmission indirectly by inhalation or settling of particles that arise from secondary reservoirs of infection on floors, bed clothing and so forth and remain suspended in air for only short periods

Control of contact and droplet infection must be directed toward individual activity and behavior. Control of droplet nuclei and dust requires attention to the environment. Methods that are applicable to the patient and may be employed in the industrial medical department are considered first.

#### PREVENTION OF SPREAD BY CONTACT

Prevention of transmission by contact comprises three phases: isolation and general measures of personal hygiene, maintenance of individual immunity by means of education, selective individual examination and interviews, vitamins and vitamin supplements and immunization procedures, and dispensary treatment of early cases.

##### *Isolation and Personal Hygiene*

The time-honored advice given to a patient with an acute respiratory infection to "go to bed for twenty-four or forty-eight hours" is undoubtedly of merit. In the absence of fever it is questionable whether or not such a procedure shortens the duration of the infection, but it serves to isolate the patient and thus to prevent spread by contact. Isolation, or two days at home in bed as a mandatory procedure, although ideal from a control point of view, is not always practical in industry. In the absence of profuse nasal secretion, cough or fever, it is probably unnecessary. The observance of general hygienic measures, such as the use of disposable tissues for coughing, sneezing and nose blowing, and cleanliness of the hands, requires no comment.

##### *Maintenance of Individual Immunity*

Individual immunity concerns that rather vague, indefinable but commonly used term "resistance." Sargent and his associates,<sup>9</sup> in a study of 721 otherwise healthy preparatory-school students during the several years of their residence at the institution, found that each boy tended to contract the same number of colds every year, individual boys varying significantly from one another in the number of colds experienced. Sargent et al. attempt to explain this observation by assuming the existence of some "constitutional factor" in the etiology of the common cold in addition to the infecting viral agent. Cannon,

Chase and Wissler<sup>10</sup> believe antibodies to be specifically modified humoral globulins whose formation is dependent on protein intake and reserves. A definite decrease in specific antibody production in animals on a prolonged low-protein diet was observed, followed by a restoration to normal levels after ingestion of adequate amounts of protein hydrolysates or of amino acids. These observations have been shown to be applicable to man as well as animals. It is likely that unknown constitutional factors, diet and numerous other complex variants contribute to the sum total of resistance. Individual resistances are probably as varied as facial configurations or fingerprints. Efforts to maintain a worker in the best possible health — to "keep his resistance high" — therefore seem to have considerable justification, especially since no methods of specific treatment or protective immunization are to date available for the large majority of acute respiratory diseases.

Methods of maintaining individual immunity are as follows:

Education may be accomplished in industry by the use of posters, pamphlets and articles in company organs in which personal hygiene, proper clothing, nutrition, exercise and rest are stressed.

Physical examinations and interviews with chronic absentees or so-called "repeaters" frequently produce favorable results. Chronic states of ill health, such as moderate secondary anemia and focal infections, are often discovered and can be corrected.

Vitamins are mentioned only because of the intense promotion by commercial manufacturers of this supposedly effective method of increasing resistance to infections of all types. To date, no scientific evidence that additional vitamins have any immunologic value in the presence of a diet that supplies the minimal daily requirements of these accessory food factors has been presented. Glickman and his co-workers<sup>11</sup> at the University of Illinois demonstrated that the effects of repeated prolonged exposures to cold were no different in healthy young men on a basal diet with borderline amounts of the water-soluble vitamins from those in subjects fed supplementary vitamins in addition to the basal diet. Bransby et al.,<sup>12</sup> in an experiment with school children aged five to fourteen, in which half were fed supplementary vitamins and half given placebos, concluded that the vitamin supplement had no apparent consistent effect on "growth, strength, endurance, fatigue potential, incidence or severity of clinical conditions, hearing and absenteeism from school." It therefore seems that education regarding proper diet is a much more valuable and much less expensive procedure than providing vitamins in a handy dispensing container for all to help themselves.

\*Since droplets are not appreciably affected by any of the methods of sanitary ventilation, infection transmitted in this manner may be considered to be essentially the same as that by direct contact.

The topic of immunization procedures is included as a comment on cold vaccines, which are also extensively promoted to industrial medical departments. Influenza vaccination, which is of value, is discussed separately below. The lack of effectiveness of the cold vaccines is succinctly stated by Reimann<sup>2</sup> as follows:

The usual commercially prepared cold vaccines contain a mixture of bacteria which have nothing to do with colds, except perhaps as secondary invaders in a small percentage of cases. And even if they did there is no acceptable evidence that vaccine prevents their invasion. Extensive controlled studies by Diehl and others have shown that cold vaccines whether given orally parenterally or as a nasal spray do not prevent colds.

Experience with cold vaccines in the New England Telephone and Telegraph Company was limited to oral vaccine given to 500 employees during the winter of 1939-1940. The results of this trial convinced us that the method is of no value as a preventive measure against colds on any group basis. There are, however, a few persons who swear by oral cold vaccine and who request it routinely each year. Although by no means convinced, we are willing to concede that in an occasional case, such a procedure may have some value. Our present policy is to keep a supply on hand each winter season for anyone who may request it, but its use is not encouraged.

#### *Dispensary Treatment of Early Cases*

The question of treatment of an early case of nasal congestion or "scratchy" throat is intriguing. In this stage of invasion the average person does nothing, waiting until symptoms become more marked and the infection well established before seeking symptomatic relief. In a large metropolitan exchange employing about 1200 girls where there is a consistently high absence rate, penicillin throat spray and sulfathiazole chewing gum were made available during the past winter for use in an attempt to abort early respiratory infections. The spray was employed in a strength of 3000 units per cubic centimeter, the gum contained  $3\frac{1}{4}$  gr (0.25 gm) per portion. Not more than four pieces of gum were dispensed to any patient. The throat was not sprayed more than twice. Psychologically, the effect was excellent, the effect on absence was impossible to assess since the over-all absence rate in the company was approximately 30 per cent lower than that in preceding years — this was a "good season for colds" and as a result there was no basis of comparison. On the basis of scientific evidence there is no justification for such an experiment. However, in large groups of women there are functional factors involved in many absences due or reportedly due to respiratory infections.

#### CONTROL OF AIR-BORNE INFECTION

Transmission of infection by droplet nuclei and dust — the air-borne elements in the spread of

infection — requires control efforts directed at the environment rather than the patient. In hospitals the employment of aseptic technics and isolation precautions have been effective in preventing cross-infections and wound contamination. In factories, offices, military barracks and schools, such methods cannot be adopted. Industry must therefore rely upon air sanitation and sanitary ventilation as the only other available methods of environmental attack. Sanitary ventilation is defined as the disinfection of air by actual ventilation or its equivalent.<sup>3</sup> Air sanitation refers to methods of engineering for the prevention and removal of air contaminants such as dust, bacteria and other noxious agents. Under these two quite similar classifications, the following methods are discussed: simple ventilation, ultraviolet irradiation, germicidal vapors, and oiling of floors (and blankets).

Simple ventilation, as accomplished by open windows, forced air circulation by fans, air conditioning and the like, does have some favorable effect in diluting contaminated air. However, it has been shown that it is not very efficient in reducing the bacterial content of air in an enclosed space.<sup>12</sup>

Ultraviolet irradiation has had extensive trial in military barracks during the past few years. The effects of upper-air and floor irradiation were studied by the Navy Bureau of Medicine and Surgery at Camp Sampson,<sup>14</sup> the barracks being divided into those exposed to high-intensity radiation, low-intensity radiation and controls. During the period of study hospital admissions for respiratory infections were 25 per cent lower in the high-intensity group. There was no significant difference between the low-intensity and control groups.

Dust and lint particles not only are bacteria laden and thus a source of air-borne infection themselves but also, when dispersed into the air by air currents, sweeping, walking and the like, reduce the effectiveness of both ultraviolet irradiation and germicidal vapors.<sup>15</sup> In studies at Fort Bragg, the oiling of floors and bedding (petroleum distillate for floors and mineral oil, and Triton NE, a neutral detergent for bedding) produced from 75 to 90 per cent fewer organisms than those observed in the untreated barracks. However, during the period when the incidence of respiratory infections was high, the large majority of which were "ARD," there was no significant difference in the number of hospital admissions between the treated and the untreated barracks.<sup>15</sup> Employment of ultraviolet irradiation in conjunction with dust-control measures produced no advantage over the use of ultraviolet light alone so far as hospital admissions for respiratory infections were concerned.

In the field of germicidal vapors, the glycols, lactic acid and hypochlorous acid gas have been employed. Lactic acid, although exerting a lethal effect on air-borne bacteria, has an unpleasant odor. Hypochlorous acid gas requires a high relative

humidity and is also corrosive to metals. The glycols depend for their action on their hygroscopic rather than their chemical properties,<sup>15</sup> and to be effective they must be maintained at near saturation levels. Tri-ethylene glycol is superior to propylene glycol in that it does not condense so readily on walls and windows.<sup>17</sup> The glycols require relative humidities of from 40 to 60 per cent for maximum effectiveness. Uniformity of dispersal is also a problem, and the range between effective saturation and fogging is very close. Paints also become sticky after several hours of exposure. In an evaluation of these methods, the Subcommittee for the Evaluation of Methods to Control Air Borne Infections, in its report to the Epidemiology Section of the American Public Health Association in November, 1946, concluded as follows:

The general use of ultraviolet irradiation or disinfectant vapors in schools, barracks and in specialized industrial environments is not justified at the present time. There is great need for further carefully controlled field studies to define mechanisms of the spread of infectious disease among these types of populations.

There is no justification for the indiscriminate use of ultraviolet light or other methods for disinfecting air in homes, offices, or places of public congregation.

An additional fact that should be kept in mind with any method of environmental control as applied to industry, no matter how completely perfected and effective the method may be, is that the worker spends only about a third of his time in his industrial environment. It avails little to work all day in a sanitary atmosphere and then catch cold riding home in a crowded streetcar or later while sitting in a crowded theater.

#### INFLUENZA VACCINATION

Although identification of a virus as the infectious agent in human influenza was made as early as 1933,<sup>18</sup> progress in developing a vaccine for immunization was slow, owing to numerous technical difficulties of culture and concentration. In 1943 the Commission on Influenza undertook extensive trials of vaccination on more than 6000 students in the Army Specialized Training Program in scattered areas of the United States. The vaccine used in this project consisted of a combination of both the PR8 and Weiss strains of virus A and the Lee strain of virus B.<sup>19</sup> As a whole, the incidence of influenza observed among the inoculated was only 31 per cent of that occurring in the controls—a morbidity rate of 2.22 as compared with one of 7.11 per cent.<sup>20</sup> Since that time numerous other studies by members of this commission have indicated the effectiveness of influenza vaccination as an immunizing procedure. From the standpoint of use in industry, some important questions present themselves. These are the hazard of fatal or severe anaphylactic reactions, the amount of absenteeism resulting directly from local or constitutional reactions to the vaccine, the possible development of a

sensitivity to egg protein as the result of vaccination, thus making subsequent vaccinations of the same person a hazardous procedure, and the optimum dosage and mode of administration.

Studies of the periodicity of influenza made it appear likely that an epidemic of influenza A would occur during the winter of 1946-1947.<sup>7</sup> Consequently, the question of vaccination of employees of the Bell Telephone System was considered during the late summer of 1946.

The programs that were adopted varied considerably among the associated companies. In the New England Telephone and Telegraph Company, a very conservative attitude was taken. Vaccination was made available to all employees who had access to the medical offices at Boston and at Providence, Rhode Island. The employees were advised of this fact, but the subject was not promoted. However, to be prepared in the event of a serious outbreak, a program was also established whereby every employee could, if he wished, obtain vaccination from his own physician at company expense. This program was distributed to all supervisory personnel to be held and placed in effect only upon advice from the medical department that influenza was beginning to occur in serious or epidemic proportions. This seemed to be the only practical method to adopt, since employees are scattered throughout the smallest towns and largest cities of Maine, New Hampshire, Vermont, Rhode Island and Massachusetts. Although a mild wave of influenza A appeared in the United States in late March, 1947, New England was not affected except for a few sporadic cases. Consequently, this program was not placed in effect. As of April 26, 1947, the United States Public Health Service reported

There have been no extensive outbreaks of Influenza in New England, the Middle Atlantic States or North Central States areas this season (since January 1947). The largest increases this year over last occurred in the South Atlantic, South Central Areas and in Iowa, Kansas and Colorado. Influenza now is apparently on the decline throughout the United States.

As a result of our conservatism, only 1585 vaccinations were given in the New England Telephone Company. Throughout the Bell Telephone System, however, fourteen other associated companies participated in the program, resulting in a grand total of 120,704 vaccinations accomplished. Of this number, no fatalities and no anaphylactic or other serious reactions were reported. A single dosage of 1 cc of the vaccine given subcutaneously was the method of administration in all cases.

In two companies with the same geographical distribution of personnel, an attempt was made to evaluate the results obtained from vaccines prepared by different methods regarding both antibody levels obtained and the number of reactions encountered.

In Group 1, 3167 subjects were given vaccine prepared by the calcium phosphate precipitation

method, 2853 in Group 2 were given vaccine prepared by the red-cell adsorption method, the so-called "Army type." Questionnaires were distributed to approximately a third of each group at the time of vaccination. Of the total number vaccinated in Group 1, 310, or 10 per cent, returned their questionnaires. In Group 2, 390, or 14 per cent, replied. Of those reporting in Group 1, there were 34 per cent local and 28 per cent general reactions. In Group 2 there were 33 per cent local and 48 per cent general reactions. Antibody titers were done on samples of both groups, and in both there was an effective antibody response, the serum antibody levels being somewhat lower in Group 1 than in Group 2. On the basis of this rather limited study, it appears that the vaccine prepared by the calcium precipitation method produced effective antibody rises with a much lower incidence of constitutional reactions. The effect of vaccination as a cause of absenteeism in the same groups was not significant. Records of day-to-day absence obtained from the operating departments showed no appreciable increase during the vaccination period. The effect of vaccination on absenteeism due to influenza has not been evaluated to date owing to the late occurrence of influenza in 1947, together with other recent disturbances within the industry.

Because a few serious anaphylactic reactions have followed vaccination of persons allergic to egg protein, it is probably wise to withhold vaccination from anyone with such a history. However, the question also arises regarding the possibility of development of such an allergy as a result of influenza vaccination. Plummer,<sup>21</sup> of New York, who has had considerable experience with the influenza-vaccination problem, believes such a development to be extremely unlikely. A review of the literature fails to reveal a report of any such occurrence. It is, however, a problem still to be determined.

Until recently, 1 cc of vaccine given subcutaneously either as a single dose or as two doses of 0.5 cc each, with an interval of seven days, has been accepted as the standard mode of administration.

Recently new interest in this aspect of the problem has been aroused by the report of Van Gelder and his associates<sup>22</sup> on the effectiveness of intradermal vaccination. In their experiments 1953 men were divided into four groups. One group received 1 cc subcutaneously, one received 0.1 cc intradermally, one received 0.1 cc intradermally repeated at the end of two weeks, and the final control group received merthiolate in a 1:40,000 solution intradermally. Serum antibody titers were determined at the time of vaccination, at the end of two weeks and again in one month. The greatest rise in titer was observed in the group receiving a single dosage of 0.1 cc intradermally. Within a month the serum antibody titer had reached a level several times

that produced by a subcutaneous injection of 1.0 cc. More recently, a group of 300 nurses were vaccinated, half of them receiving a subcutaneous injection of 1 cc and the other half receiving 0.1 cc intradermally.<sup>21</sup> Antibody titers were determined on the entire group. In both, effective antibody rises occurred but were found to be slightly higher in the group receiving 1 cc subcutaneously.

Enders<sup>23</sup> has recently given a small series of patients vaccine intradermally diluted in 1.5 parts with physiologic saline solution, 0.1 cc is then given so that the patient receives only 1/50 of 1 cc of this vaccine. In persons with relatively low serum antibody levels prior to vaccination, the antibody response was good, increasing approximately twenty times against virus A and some eight or nine times against virus B. In subjects with high titers prior to vaccination, there was very little increase in the antibody levels.

Although to date there have been no reports to indicate that influenza vaccine of itself produces a sensitivity to egg protein in a person not previously sensitive, such an effect remains a possibility. The intradermal method, therefore, seems to possess the advantage of lessening the hazard of anaphylactic reactions. This method also requires less vaccine and in large groups reduces the expense of vaccination considerably. From the standpoint of vaccination of large groups, however, the subcutaneous method possesses a slight advantage, since it requires less time. If 0.1 cc of vaccine subcutaneously produced an effective antibody rise, this would probably be the optimum dosage and mode of administration.

A final point regarding the advisability of influenza vaccination for the season of 1947-1948 is that the more or less mild outbreaks of the past two winter seasons have served to upset to some extent the future predictions of influenza as based on its past periodicity. It therefore remains uncertain whether an epidemic will or will not occur during the coming winter season. I understand that in the recent outbreak of influenza, definitely identified as due to virus A, vaccination of 10,000 university students at one institution was accomplished. Satisfactory serum antibody levels against virus A were obtained, but no protection was afforded. This suggests the possibility of some strain of virus A other than those incorporated in the current vaccines.\* If true, it will necessitate careful reconsideration of the entire problem. From the standpoint of industry, the question of whether to vaccinate or not to vaccinate is one that will have to be decided by the individual physician charged with the responsibility of the health of his own industrial population. In our company no definite plans for the winter season of 1947-1948 have as yet been formulated.

\*Subsequently identified as the "Rhodes" strain.<sup>24</sup>

## SUMMARY

The problem of acute respiratory diseases in industry is essentially the same as that in the general population

Possible methods of control that may have some application in industry are reviewed

To date, no effective methods of control have been achieved

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## THE COURSE OF RHEUMATOID ARTHRITIS IN PATIENTS RECEIVING SIMPLE MEDICAL AND ORTHOPEDIC MEASURES\*

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NO METHOD of treatment thus far employed in rheumatoid arthritis can justly be considered "specific"—a term that implies a rapid and complete reversal of subjective and objective manifestations of the disease, whether localized in the skeletal system or in other parts of the body. Such a therapeutic principle, of course, is constantly effective and leaves no doubt of its value in the minds of either patient or physician. Pending the discovery of this long-awaited advance, the treatment of rheumatoid arthritis is necessarily confined to measures believed to be useful but of unproved value. Furthermore, the assessment of newer methods of treatment is always difficult because of the paucity of information concerning the clinical course of rheumatoid arthritis as judged by a large group of patients treated with conservative, generally employed procedures for a number of years. It is the purpose of this report to review briefly such series already described in the literature and to present in detail

the results of a long-term follow-up study of 250 patients receiving simple medical and orthopedic measures.

Whereas almost every description of rheumatoid arthritis includes general statements regarding observations on the course pursued by patients, numerical studies are relatively few.<sup>1-12</sup> In addition, nearly all investigations fail to give sufficient information for use for comparison with other series or for evaluation of new therapeutic measures. In some reports the number of patients studied is obviously too small, and in others the duration of follow-up study is not stated or is limited to months rather than years. With one exception,<sup>12</sup> the cases included have not been subdivided into sex, age, previous duration of the disease, severity of the arthritis and other factors that might influence the results. The degree of improvement has rarely been rigidly defined, patients showing slight improvement being sometimes lumped together with those in remission and subjective gain or increase in functional capacity instead of clear-cut objective changes being utilized as criteria. Some series even contain types of joint disease in addition to rheumatoid arthritis and should of course be eliminated from consideration. A recent, informative article by Steinbrocker<sup>13</sup> presents a further discussion on the

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expression of therapeutic results in rheumatoid arthritis

The series reported below is based upon 300 unselected patients with rheumatoid arthritis admitted to the medical wards of the Massachusetts General Hospital between 1930 and 1936. They represent consecutive hospital admissions with the exception that no children under twelve years of age were studied, since they were handled on a separate pediatrics service. The diagnosis in these cases was based on the usual clinical criteria, but all stages of the disease were included. Since some of the patients were in a mild or atypical phase, the absence of either symmetrical phalangeal-joint involvement, x-ray changes or an increased sedimentation rate was not considered a ground for exclusion from the series. Thirty-eight patients with rheumatoid spondylitis (although some authors consider this an independent type of arthritis) were not rejected, especially since the majority had peripheral joints affected in addition to the spine and sacroiliac joints. Other joint conditions, however, such as specific infectious arthritis, gouty arthritis, rheumatic fever and degenerative joint disease, were carefully excluded. In a few patients the passage of time made it clear that the original diagnosis had been erroneous, so that 7 cases were excluded, the number being reduced to 293. Twenty-one patients were also eliminated because they had received special forms of therapy, either vitamin D in massive dosage or gold salts, and 22 because follow-up studies were inadequate. The remainder, 250 in number, form the subject of this report.

The patients were rarely kept in the hospital for more than three or four weeks, for diagnosis and accumulation of clinical and laboratory data and to receive instruction in and a brief trial of therapy. This consisted largely in measures that could be continued at home, including rest periods, analgesics, exercises, application of heat to affected joints, an adequate diet with supplementary vitamins and orthopedic procedures when indicated. Fever therapy, in which we were interested at the time,<sup>14</sup> was given to 52 patients, and 16 received blood transfusions, but neither group did better than the remainder. Removal or treatment of foci of infection was carried out in 75 patients, the rate of improvement approximating that attained in patients in the series not so treated. Thirty-eight patients were rehospitalized for periods of three months or over one or more times in the course of their illness. As might have been expected, they had severer disease, which was not doing well, and ultimate improvement was evidenced in only 29 per cent.

Our original plan for follow-up study was to have each of the patients seen in the clinic at least once or twice a year. But regularity of attendance naturally depended upon their need or willingness to return or, for patients living at a distance or markedly disabled, their ability to make the trip.

Certain patients were thus unavoidably seen at irregular intervals. We were aided in receiving reports about absentees and in getting them back to the clinic by trained follow-up workers and by nurses attached to the departments of public health in Massachusetts and other New England states. The small number who had left New England were kept in touch with by letter, but none were accepted.

TABLE 1 Follow-up Study of 250 Patients with Rheumatoid Arthritis

DURATION OF OBSERVATION	NO. OF CASES	PERCENTAGE
yr		
1 or less	14	5.6
3 to 1	9	3.6
5 to 3	77	30.8
10 to 5	80	32.0
15 to 10	114	45.6
More than 15	6	2.4
Total	250	

as improved unless the evidence was definite and none classified as in remission without examination in our clinic. The duration of observation of the patients after discharge varied from six months to sixteen years, with an average of nine and a half years (Table 1). Thus, 200 patients, or 80 per cent, were followed for more than five years. Because of the length of the follow-up period and because many patients were in the older age groups, 56 died in the course of the study, principally from causes unrelated to the arthritis. The results in such cases are expressed according to the latest examination before death.

The status of our patients, according to the most recent information available up to April, 1947, is expressed in Table 2. They are divided into three

TABLE 2 Results in 250 Patients with Rheumatoid Arthritis Receiving Simple Medical and Orthopedic Measures

STATUS OF DISEASE	NO. OF CASES	PERCENTAGE
Improved:	133	53.2
In remission	38	15.2
Moderately improved	43	17.2
Slightly improved	52	20.8
Stationary	32	12.8
Worse	45	18.0
Total	250	

main groups, the base line in all cases being the patients' condition on admission to the hospital. The first group has also been subdivided according to the degree of improvement exhibited. In following the patients, we did not rely upon a set scheme with numerical values assigned to various clinical and laboratory findings.<sup>15, 16</sup> At the time of each observation of the patient, however, subjective and objective



findings pertinent to the clinical course were carefully recorded. Detailed examinations of the articular system, as well as complete general physical examinations, were made at frequent intervals. From 1931 on, sedimentation rates were determined at nearly every return visit to the clinic. Further aid in evaluating the patients' progress was furnished by other laboratory tests and by serial roentgenograms of the joints.

In the group labeled in remission in Table 2, the disease was inactive, the patients asymptomatic

TABLE 3 *Results according to Sex*

STATUS OF DISEASE	MALE PATIENTS		FEMALE PATIENTS		DIFFERENCE
		%		%	
Improved		58.4		50.0	8.4 ( $\pm 6.5$ )
In remission	15	9	14	7	
Moderately improved	18	1	16	7	
Slightly improved	24	4	18	6	
Stationary		13.8		12.2	
Worse		27.8		37.8	

and examination of the joints negative except for residual deformity in a few cases. In all cases, the sedimentation rate as determined by the Rourke-Ernstene<sup>17</sup> method was normal or only slightly increased. The next group, with moderate improvement, showed noteworthy subjective and objective gain but, while approaching this state, could not justly be called in remission. Those judged slightly improved manifested definite objective changes of a favorable nature, and subjective improvement was also present but less marked. Gain in joint function due to conservative or operative orthopedic pro-

TABLE 4 *Results in Patients with and Those without Spondylitis*

STATUS OF DISEASE	PATIENTS WITH SPONDYLITIS		PATIENTS WITHOUT SPONDYLITIS		DIFFERENCE
		%		%	
Improved		44.8		54.6	9.8 ( $\pm 8.7$ )
In remission	2	6	17	4	
Moderately improved	18	5	17	0	
Slightly improved	23	7	22	2	
Stationary		18.5		11.8	
Worse		36.7		33.6	

cedures was not in itself classified as improvement. The patients of the stationary group were essentially unchanged when last seen, but at least half had previously pursued a fluctuating course, with periods of both exacerbation and improvement. Those with minor variations in symptomatology and joint findings were also included under this designation. The classification "worse" requires little explanation. It includes some patients who were subjectively better and even less disabled, but the disease had progressed as determined by physical

examination and roentgenograms. Conversely, 4 patients who showed marked lessening of activity of the arthritis, but no change in function of the joints or even decreased motion in some, were put into the slightly improved group. Of the patients classified as worse, only 14 per cent were working, 41 per cent were ambulatory, and the remaining 45 per cent (15 per cent of the entire series) were confined to bed or wheel chair.

As mentioned above, there are few reports in the literature on the continued observation for one or more years of comparable series of patients with rheumatoid arthritis. Three may be cited briefly: 77 cases studied by Pemberton and Peirce,<sup>2</sup> 274 by Thompson, Wyatt and Hicks<sup>7</sup> and 253 by Fletcher and Lewis-Faning.<sup>12</sup> In the first, 90.9 per cent of patients showed some degree of improvement, and 22 per cent were considered to be in remission, the figures were 87.2 per cent and 6 per cent, respectively, in the second and 64.4 per cent and 24.6 per cent in the third. There is thus a wide variation in the percentages given for improvement but a general agreement with our own series that a small minority of patients are likely to enter upon a sustained remission. In addition, Sashin, Spanbock and Kling<sup>8</sup> state that 15 per cent of their 120 patients "improved markedly" — a proportion that happens to coincide exactly with those found in remission in our series. Without additional information about differences in prognostic factors, including age and sex of the patients and duration and severity of the arthritis, further discussion of variations in results appears unprofitable. Of more interest, perhaps, are the data obtained from the first follow-up study of the same series of patients, conducted in 1937.<sup>18</sup> At that time the patients suitable for analysis numbered 274. Of these, 145, or 52.9 per cent, showed some degree of improvement, with 16.4 per cent in remission — figures almost exactly the same as those obtained at present but not necessarily representing the same patients. In the past ten years, however, there has been a significant increase in the "worse" group from 18.3 to 34.0 per cent at the expense of those considered stationary, who decreased from 28.8 to 12.8 per cent.

The series presented in this paper was made up of 94 male and 156 female patients. Table 3 demonstrates that the difference in outcome between the two sexes was not significant, although the males did slightly better. At this point, it seemed useful to eliminate any possible influence on these results of the 38 patients with spondylitis, 33 (87 per cent) of whom were males. Table 4 shows no difference of statistical significance between those with and those without spinal involvement, although only 1 patient with spondylitis was considered to be in remission. A similar conclusion is reached in another paper,<sup>19</sup> in which 64.4 per cent of 253 patients with peripheral rheumatoid arthritis showed improvement of some degree compared to 55.8 per cent of 52 patients with

spondylitis. In Table 5, the 38 patients with spondylitis have been excluded from consideration, bringing the number of males down to 61 and that of females to 151. In this table there is a significant difference in favor of males. Since we have been unable to find data in the literature confirming this finding, the results can only be considered suggestive until further evidence is available.

The majority of those expressing an opinion regarding the influence of the patients' age on the

TABLE 5 Results in Male and Female Patients Excluding Those with Spondylitis

STATUS OF DISEASE	MALE PATIENTS		FEMALE PATIENTS		DIFFERENCE
	No.	%	No.	%	
Improved:					
In remission	22	68.9	15	48.9	70 ( $\pm 7.5$ )
Moderately improved	21	3	15	2	
Slightly improved	24	7	18	5	
Stationary		9.8		12.6	
Worse		21.3		18.5	

course of rheumatoid arthritis believe that older persons tend to do better.<sup>19-21</sup> The one exception encountered has been Schnell,<sup>22</sup> who states that the prognosis is much worse in cases starting after the age of fifty-five. In the present series, no significant differences regarding the age at onset of the disease were found between older and younger patients. When the age on admission to the hospital was taken into consideration, however, patients thirty-nine years of age or younger showed a greater degree of improvement than those forty years or over. The results are presented in Table 6, in which 133 patients in the younger group are compared with 117

TABLE 6 Results in Patients under and over Forty Years of Age on Admission

STATUS OF DISEASE	PATIENTS UNDER 40		PATIENTS OVER 40		DIFFERENCE
	No.	%	No.	%	
Improved:					
In remission	21	0	8	5	19.8 ( $\pm 6.3$ )
Moderately improved	20	3	14	5	
Slightly improved	20	3	18	8	
Stationary		9.8		17.2	
Worse		28.6		41.0	

in the older. Again, only tentative conclusions can be drawn in the absence of corroboration from other series.

The most striking factor apparently affecting prognosis was found to be the duration of the disease. As pointed out in Table 7, nearly three quarters of the 81 patients with duration of arthritis before admission of one year or less showed some degree of improvement, and 37 per cent were in remission. Table 8 demonstrates an even higher percentage of

improvement in patients seen within the first six months, whereas the outcome of those whose onset dated back more than one year was not related to the duration of the disease. That the results are

TABLE 7 Results according to Duration of Arthritis

STATUS OF DISEASE	DURATION BEFORE ADMISSION		DIFFERENCE
	1 YR. OR LESS	MORE THAN 1 YR.	
	No.	%	
Improved	73	9	30.2 ( $\pm 7$ )
In remission	37	0	4.7
Moderately improved	23	3	14.2
Slightly improved	13	6	24.8
Stationary		8.6	14.8
Worse		17.5	41.5

better in patients treated early has frequently been stated without evidence derived from numerical studies.<sup>8, 11, 21, 22-25</sup> In one paper this point has been subjected to careful statistical study in a series of 254 patients, with the conclusion that there is a suggestion that the percentage of success is higher in patients with disease under one year's duration.<sup>12</sup>

TABLE 8 Improvement according to Duration of Arthritis before Admission

DURATION	PATIENTS IMPROVED	
	No.	PERCENTAGE
Six months or less	53	81.0
Twelve to six months	28	60.6
Three to one year	64	45.3
Five to three years	35	34.3
Ten to five years	39	48.7
Over 10 years	31	41.9
Total	250	

Figures presented by Cecil and Archer<sup>1</sup> are comparable to those in Table 8, with 82 per cent of their patients treated in the first six months of their disease either recovered completely or greatly improved. Even more striking results are reported by Steinbrocker<sup>23</sup> in 366 patients with "acute rheumatoid arthritis." Approximately 90 per cent were

TABLE 9 Results according to Type of Involvement

TYPE OF INVOLVEMENT	No. OF PATIENTS	
	No.	PERCENTAGE
Symmetrical from onset	150	56.0
Asymmetrical becoming symmetrical	45	40.0
Asymmetrical on admission	17	81.3
Spondylitis	38	44.8
Total	250	

discharged as recovered within three months of admission. Although frequently neglected, these findings should always be taken into consideration in the evaluation of methods of therapy.

The patients with arthritis in the peripheral joints alone were divided into typical symmetrical cases, with involvement of at least one pair of corresponding joints dating back to the period of onset, those who reached this stage some time after the onset and those who were still atypical upon admission. The percentage of improvement in each group, as well as in those with spinal involvement, is shown in Table 9. Although too small in number to warrant conclusions, the asymmetrical group did unusually well, in accordance with previously recorded clinical impressions<sup>20, 26, 27</sup>. Patients without spondylitis were also classified according to the extent of joint involvement (Table 10). There was a marked difference in outcome between those with mild and those with extensive disease. In the same table, a comparable analysis has been made of the degree of activity of the arthritis with both constitutional and articular manifestations included under this

TABLE 10 Results according to Degree of Joint Involvement, Activity of Disease and Total Severity of Process

CHARACTERISTICS OF DISEASE	NO. OF CASES	PATIENTS IMPROVED %
Joint involvement*:		
Mild	75	70.5
Moderate	96	51.2
Extensive	41	19.4
Activity		
Mild	51	76.3
Moderate	136	59.6
Marked	63	20.6
Total severity		
Mild	59	79.7
Moderate	150	51.3
Marked	41	21.8

\*Excluding patients with spondylitis.

heading. Again, the patients with mild activity showed a much higher percentage of improvement than those whose activity was classified as marked. The next heading in the table, "total severity," requires explanation. This was estimated for each patient by two or more observers on the basis of his condition on admission. The factors taken into consideration included the degree of constitutional symptoms and signs, the speed of progression of the disease, the amount of disability, the extent of involvement and the activity of the process. As might be surmised from the results in the two preceding groups, a striking contrast is evident between cases of mild and those of marked total severity. The nearest approach that we have encountered to a similar analysis has been made by Sclater,<sup>28</sup> who divided 388 patients with rheumatoid arthritis into four groups according to the severity of the disease. Milder cases were more numerous among those one year or less in duration, with the opposite found in patients who had suffered from arthritis for four years or more. Although no figures are given, the statement is made that the outlook is very much

worse for patients with disease of marked severity. Similarly, most cases in our series with disease of one year's duration or less and accordingly with a more favorable prognosis were of mild or moderate total severity.

A number of factors that were apparently of no importance in determining the patients' course are listed in Table 11. These included a history of pro-

TABLE 11 Prognostic Factors Apparently not Important in Results

FACTORS	PATIENTS IMPROVED %
Prodromal symptoms	52.5
No prodromal symptoms	53.8
Intermittent course before admission	50.0
Progressive course before admission	54.4
Acute onset	60.3
Gradual onset	51.0
Red-cell count below 4,000,000	56.3
Red-cell count 4,000,000 or above	52.6
Family history of rheumatoid arthritis	45.0
No family history of rheumatoid arthritis	54.3
Family history of rheumatic fever	50.0
No family history of rheumatic fever	53.5
Onset within two years of menopause	46.2
Female patients without onset within two years of menopause	50.8

dromal symptoms before onset, an intermittent rather than progressive course before admission and an acute contrasted with a gradual onset. Others were a severe degree of anemia, a family history of rheumatoid arthritis or rheumatic fever and, in women, onset within two years before or after the menopause. There was no significant difference in outcome between those with weight loss of any degree and the remainder. However, out of 27 patients who weighed on admission 79 per cent or less of the average for their age, sex and height, only 26 per cent showed improvement. Four authors<sup>6, 23, 26, 29</sup> agree that poor nutrition evidenced by weight loss is a poor prognostic sign, but our figures fail to corroborate the reported influence of a family history of rheumatoid arthritis,<sup>30</sup> anemia,<sup>28</sup> the menopause,<sup>20</sup> an intermittent course before admission<sup>23</sup> or an insidious in comparison with an acute onset<sup>20, 26</sup>.

When a series like the present one is used in comparison with groups of patients receiving special methods of treatment, the argument may be raised that, although the proportion of patients in each series ultimately showing improvement may be approximately equal, the specially treated group improves much more rapidly. Since our patients were not observed at regular intervals, it is impossible to calculate the rate of improvement in all those finally so recorded. Certain available data, however, may be of assistance. Of 175 patients seen in the clinic one or more times within two years after discharge, 84, or 48.0 per cent, were considered improved, a percentage approximating that finally obtained for the whole series (Table 2). Another approach con-

cerns the 133 patients in the same table who were considered improved at the time of their most recent examination. Improvement was delayed over two years in 30 per cent of these patients and over four years in only 21 per cent, with corresponding figures of 29 per cent and 16 per cent for the 38 patients in remission. It seems fair to assume, then, that in the majority of cases improvement was reasonably rapid but that partial or complete remissions can be looked for in a certain proportion of patients even after several years of discouraging failure to gain.

The variable course of rheumatoid arthritis, marked by periods of exacerbation and improvement at irregular intervals, has often been stressed.<sup>21, 22, 23, 24</sup> Such a course was noted in about half the patients in each group in Table 2 whether finally considered improved, stationary or worse. An additional example of this tendency is given in Table 12, which demonstrates that nearly half the patients who gave promise of early improvement of any degree sooner or later relapsed. A certain number of these, as shown in the table, subsequently improved. The net relapse rate of 34.6 per cent can be compared with a rate of 28 per cent obtained from a combined series in the literature of 768 patients originally showing improvement under gold therapy. In view of the "fluctuant life cycle"<sup>25</sup> of rheumatoid arthritis, "remission" or "arrest" is a more suitable term than cure. If the last is used, it should be prefaced, as in cancer statistics, by the number of years the patients have been observed with the disease in an arrested state. At present, the figure for "five-year cures" in the series is 23 patients, or 9.2 per cent—slightly higher than the 6.3 per cent recently reported for 142 patients given gold therapy.<sup>22</sup>

### DISCUSSION

It is obviously impossible to collect a true control series of untreated patients with rheumatoid arthritis. Nearly every patient with the disease in a recognizable form has received some form of therapy, whether advised by his physician, by an unorthodox practitioner or by a member of his family. We are forced to depend upon groups of patients like those in the present series, who received simple measures generally believed to be helpful or, at times, methods of treatment later proved to be of doubtful value. It is hoped that additional series will be collected and published for comparison with this one and with results attained by special forms of therapy. Certain important principles that should be followed in the selection and analysis of the patients under observation have already been outlined but may be presented here in summary form.

No avoidable form of selection should be used, and, if possible, the patients should represent consecutive admissions to a clinic or hospital. In this way, a wide variety will be under observation, and the series will not be limited to certain types or stages of the disease. The follow-up period should

be spread over years rather than months to allow for the usual relapses and remissions. When the time has come for the evaluation of results, certain factors of prognostic implication should be taken into consideration. These include, at a minimum, the age and sex of the patients, the duration of the disease, the type and extent of involvement and the activity and severity of the process. Improvement should be graded according to degree, with no patients included as improved unless objective articular changes of a favorable nature have been recorded. It is desirable, of course, that a uniform scheme for the evaluation of therapeutic results eventually be adopted.

The results in the present series indicate that about 50 per cent of comparable patients will ultimately

TABLE 12. Relapse Rate of Patients Who Improved within Two Years

STATUS OF DISEASE	No. OF CASES	PERCENTAGE
Improvement within two years	84	—
Later relapses	39	46.5
Complete	31	37.0
Partial	8	9.5
Subsequent improvement	10	—
Relapse on last follow-up examination	29	34.6

imately improve. Since it is planned to keep them under observation as long as possible, this percentage may well change in the course of time. The percentage obtained at present is below "the inevitable 75 per cent improvement"<sup>26</sup> usually mentioned in estimates on the prognosis in rheumatoid arthritis.<sup>26, 27, 28</sup> A milder, strictly ambulatory group might do better, but, as shown in Table 10, the disease was of marked severity in only one sixth of the patients. If the estimated speed of improvement seems less than that in patients treated, for example, with gold, the incidence of relapse in gold-treated patients (75 per cent in one series<sup>29</sup>) must also be taken into consideration. It should finally be made clear that the purpose of this paper is not to claim beneficial results from the conservative routine employed in these patients. Although such methods are generally believed to be helpful, no proof is available that they alter the natural course of the disease.

In addition to presenting the course of the 250 patients to date, an attempt has been made to demonstrate which clinical or laboratory findings are of value in suggesting the outcome. The list studied is by no means exhaustive, and other, more important factors may eventually come to light. With the present evidence, one might assemble a composite patient who would be likely to do well as follows: a man, under forty, with disease of less than a year's duration, of normal or nearly normal weight, with mild joint involvement, preferably asymmetrical, slight activity and mild total severity.

## SUMMARY

Two hundred and fifty unselected patients with rheumatoid arthritis who received simple medical and orthopedic measures have been under observation for an average period of ten years

Over 50 per cent evidenced a definite degree of improvement when last seen, and 15 per cent were considered in remission

Certain factors of prognostic value outlined deserve consideration in the future reporting of therapeutic results

The use of control series of this type seems necessary to determine the effect of nonspecific measures employed in the treatment of rheumatoid arthritis

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## ANESTHESIA IN THE SURGICAL TREATMENT OF BRONCHIECTASIS\*

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THE anesthesia and operating-room care of patients who are to be treated surgically for bronchiectasis need to be planned and carried out in a simple but logical manner if anesthesia mortality and postoperative complications are to be held to a minimum

Since the advent of penicillin nebulization in the preoperative preparation of these patients, the anesthetic procedures have been simplified considerably. Most patients now come to surgery with comparatively "dry lungs" as compared with those who did not receive the benefit of penicillin therapy by inhalation. It is my belief that bronchoscopy should not be performed immediately before operation, since most of these patients become rather poor

anesthetic subjects. First of all, the patient who is bronchoscoped under topical anesthesia becomes quite disturbed emotionally and is therefore difficult to anesthetize. Bleeding from the tracheobronchial tree is not unusual and certainly complicates the induction and maintenance of anesthesia. Patients in whom bronchoscopy is performed either before or after anesthesia has been established tend to secrete large quantities of mucus from the respiratory tract. It has become a routine procedure in our clinic to spend some time with the patients before operation, explaining as carefully as possible the methods of anesthesia and the supportive measures that will be carried out during the operation to make the procedure a relatively safe one. With such reassurance, patients come to the operating room with a minimum of fear, and the whole anesthetic procedure is simplified.

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Only simple anesthetic practices are carried out. Small amounts of preanesthetic medication are given about two hours before operation. Anesthesia is induced with Pentothal given intravenously in the patient's room to mitigate emotional stress as far as possible. The excitement phase of inhalation anesthesia is eliminated when this method is used.

After Pentothal induction, nitrous oxide and oxygen in a ratio of approximately 75:25 per cent are given for a few minutes to diminish reflex activity of the pharynx and larynx. Ether is then added to the system slowly, and the Pentothal is continued until a sufficient amount of ether has been vaporized to bring the patient into light surgical anesthesia. The trachea is then intubated with a short Magill endotracheal catheter carrying an inflatable cuff. The cuff is inflated with air rather cautiously, just enough pressure to seal the airway completely being used. Two 15-gauge needles are placed in the veins, usually at the ankles. One needle is connected directly to a slow drip of whole blood, and the other is closed with a stilet but kept in place so that it can be used immediately if rapid replacement therapy becomes necessary during severe hemorrhage. The patients are usually placed in the lateral position on the operating table. The Trendelenburg position is not employed because of the increased danger of filling the upper lobe bronchus of the dependent lung with foreign material. The patients are draped in such a manner as to allow the anesthetist a completely unobstructed view of the operative site. The patients are carried in light third-stage, first-plane anesthesia. The respiratory character is watched closely, and the eyes are observed frequently for eyeball movements. If eyeball movement is not apparent the anesthesia is lightened until the eyeballs once more move when the lids are raised. A few minutes before the pleura is entered, a positive pressure equivalent to 5 or 6 mm of mercury is built up in the anesthesia system, this is done to prevent rapid collapse of the lung. The pressure is gradually released after the pleura is opened, and the lung is decompressed slowly. It is my experience that patients who have a slow decompression of the lung rarely develop mediastinal flutter and paradoxical respiration. Positive pressure is rarely required during maintenance. The tidal volume of these patients with one lung completely collapsed has been measured and in almost every case has been equal to or greater than that before anesthesia. When ether and oxygen anesthesia is being used, hilar infiltration is not necessary to lessen the dangers of severe reflex activity during manipulation.

It is necessary to aspirate the tracheobronchial tree quite frequently during operation. A catheter of sufficient length to reach the lowermost portion of the main-stem bronchi is used. In most adult patients ordinary urethral catheters are not of sufficient length, a 45-cm. catheter made from a Wangenstein

stomach tube is used in most cases. Anesthetists in our clinic are required to spend most of their time on their feet watching the operative field and at the same time keeping careful check on the patient's pulse, blood pressure and color, determining the depth and rate of respiration simply by holding the anesthetic bag in the hand. If diaphragmatic movements are observed at all times, tracheobronchial obstruction or mediastinal flutter can be detected several minutes before positive clinical signs are apparent in the character of the blood pressure and pulse and before cyanosis develops. If there is no obstruction and if the mediastinum is stabilized, the diaphragm will be seen to move with smooth, even motions. If diaphragmatic movement suddenly changes from a smooth, even contraction to a more rapid and jerky type the patient has developed either obstruction to the contralateral lung or mediastinal flutter. When this occurs the tracheobronchial tree is aspirated immediately, after which the diaphragm usually resumes its normal rhythmic movements. If the character of the diaphragmatic movements does not become normal after aspiration, a positive pressure equivalent to 4 or 5 mm of mercury is built up in the closed system to raise the mediastinum and stabilize its movements. On rare occasions it is necessary to maintain slightly positive pressure throughout the operation. Controlled respiration is never used because of the danger of gravitating foreign material causing an unrecognized obstruction in one or more of the lobes of the dependent lung. About every half hour during operation the surgeon is asked to stop his procedure for a minute or two while the unoperated lobes are re-expanded. This is done to be sure that bronchi in the uninvolved portion of the lung have not been inadvertently ligated. Re-expansion will also help the surgeon locate imperfectly developed interlobar fissures. The inflatable cuff on the endotracheal tube is decompressed several times during operation to minimize the danger of pressure necrosis.

Whole blood is given from the time the incision is made until the operation has been completed. An attempt is made to estimate as accurately as possible the amount of blood loss in each case. All blood loss is replaced as it occurs. If bleeding is vigorous the blood is allowed to run as fast as possible, and on occasion it is forced into the circulatory system under pressure. If hemorrhage is severe a second bottle of blood is attached to the stiletted 15-gauge needle previously placed in a vein for this purpose. The average patient undergoing lobectomy for bronchiectasis will lose between 1000 and 1500 cc of blood. If citrated blood is readily available and all blood loss is replaced as the loss occurs the operative morbidity and mortality are minimized. After the diseased portion of the lung has been removed the tracheobronchial tree is aspirated as thoroughly as possible. The remaining portion of the lung is

then re-expanded slowly, only enough positive pressure to accomplish the re-expansion being used. After re-expansion the positive pressure in the anesthesia system is reduced until the correct amount of pressure to maintain re-expansion is determined. This pressure is measured on a water manometer and is maintained until all layers of the chest wall have been closed. After the pleura is closed the anesthetist watches the pulse and blood pressure closely, for the amount of pressure required for re-expansion occasionally interferes with circulation once the chest wall has been tightly sutured. If there should be a sudden decrease in blood pressure with a fading pulse volume and increased pulse rate the pressure is reduced.

All anesthetists accepting the responsibility for anesthesia in major thoracic surgery should be able to pass a bronchoscope with the patient in a lateral position so that direct visual aspiration of the tracheobronchial tree can be carried out during operation if necessary. On occasion the removal of large blood clots or other foreign material that cannot be removed by catheter suction is a life-saving measure. After the chest has been closed the patient is turned on his back, water bottles are attached to the drainage tubes, and bronchoscopy is performed to be sure that all foreign material, especially blood clots, has been removed. Our postoperative bronchoscopies are always carried out in a well lighted room. Assistants are required to watch the patient's color and pulse very closely. A vigorous stream of oxygen is passed down the lumen of the bronchoscope during all bronchoscopic procedures to get a rapid diffusion of oxygen into the

patient's lungs. If for any reason the patient develops cyanosis or has a severe change in pulse or blood pressure, the bronchoscope is removed immediately. Deaths during postoperative bronchoscopy have probably been due to suffocation because the tip of the bronchoscope has been wedged into a lower bronchus for a prolonged period, completely obstructing the patient and preventing oxygenation of the remaining lung. Reflex activity probably plays little or no part in the death of these patients.

After bronchoscopy x-ray examination of the chest is performed while the patient is still on the operating table, he is not taken back to his room until the x-ray films have been interpreted. If there is evidence of pulmonary collapse to any degree bronchoscopy is again performed, and the patient is again checked by x-ray examination before being returned to his room. It is realized that many patients would get along well after operation if they were not bronchoscoped immediately postoperatively, however, it is difficult to determine which patients need bronchoscopy and which do not. Occasionally, a large blood clot or a considerable quantity of pus is removed from a patient whose tracheobronchial tree seemed free of foreign material at the end of the operation. If a large blood clot is left in a bronchus the patient may be unable to cough it up postoperatively. Severe atelectasis or death may result. In our patients x-ray examinations are made daily for the first four or five days, and the patients watched closely for evidence of pulmonary collapse. Once the slightest amount of postoperative atelectasis or tracheobronchial obstruction develops bronchoscopic aspiration is indicated.

## LOCALIZED COCCIDIOIDAL OSTEOMYELITIS

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**C**OCCIDIOIDOMYCOSIS is a disease produced by the fungus *Coccidioides immitis*, which is present in large concentration in the soil of the San Joaquin Valley, California, and to a lesser degree in neighboring states. In its adult form, it is a spherule of about 50 microns in diameter, which has a doubly refractile capsule. The portal of entry is the respiratory tract or skin. The disease has both primary and secondary phases. Ordinarily, there is a primary pneumonic focus. The nodules produced by the endospores closely resemble those of tuberculosis.

Once allergy is established, reinfection may bring out the disease in its secondary or chronic phase. However, in only a small percentage of cases does the secondary phase develop. Multiplicity of lesions is the general rule, and soft-tissue abscesses, which are common, may extend to underlying bone.

Reports indicate that the prognosis of the disease in its secondary phase is poor, the mortality being over 50 per cent.

Rest and immobilization are requisites to prevent metastatic spread of the disease. As in many of the reported osseous infections, x-ray examination in the case reported below demonstrated a wall outlined about a cavity suggestive of a bony cyst. Removal of a peripheral well advanced bone or joint infection should always be considered, because the possibility that multiple foci will develop is great.

As might be anticipated, the seasonal distribution of initial coccidioidomycosis corresponds to the dusty time of the year. The peak occurs, therefore, in the summer and fall, whereas the ebb is in the few rainy months.

Localized coccidioidal infections of bone are by no means a new entity, having been occasionally reported in the medical literature. The case presented

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below is interesting in that the patient had originally been treated as a case of pyogenic hematogenous osteomyelitis at another hospital. It was not until biopsy of the lesion that the underlying disease was demonstrated. When the patient was first seen at this institution, an oval-shaped skin ulcer over the posterior aspect of the right os calcis was present. The center of the ulcer was deeply pitted, and its bed was of a "currant-jelly-like" consistence. This fact, in addition to the exacerbations and remissions that followed combined general and local treatment of the ulcer with penicillin, led to a tentative diagnosis of tuberculosis. Subsequent laboratory studies ruled out this possibility.

It is apparent in the following report that the original chest condition of the patient, diagnosed as "pleurisy with effusion of unknown etiology," was probably a subclinical coccidioid infection.

### CASE REPORT

A 39-year-old private had enlisted in the Army at the age of 22 and enjoyed good health except for frequent head and chest colds during the winter season. At the onset of the war he was assigned to an Infantry division and served in the European Theater. From January to April, 1945 he was a prisoner of war in Germany. During that time he lost 15 pounds in weight, but he had no particular illnesses. In May he was returned to the Zone of the Interior and was given a 60-day furlough which he spent in Phoenix, Arizona. About June 1 he developed a cough, which was accompanied by fever and pain in the right anterior portion of the chest. As his condition became progressively worse, he was admitted to a nearby Army general hospital on June 15.

X-ray examination revealed a small amount of pleural fluid in the medial anterior lower right portion of the chest wall. No etiology for this pathologic state was determined, but after a course of intramuscular penicillin therapy the chest pain ceased, the chest fluid cleared, and the patient became afebrile. At the end of July he was given a 60-day furlough, during the latter part of which pain and swelling developed on the posterior aspect of the right heel without antecedent trauma. On his return to the hospital x-ray films disclosed osteomyelitis of the right os calcis, and a sanatoria was earned out. Cultures revealed a *Staphylococcus aureus*. The foot was immobilized in a plaster boot with the wound packed open. In November when the boot was changed the wound appeared clean without purulent drainage. However, in December further cultures revealed *Staph. aureus*, and he was again placed on a regime of intramuscular penicillin. X-ray films of the os calcis at that time were reported as showing "no further destruction of bone."

In January 1946, at the request of the patient, he was transferred to the Cushing General Hospital. Physical examination revealed an oval-shaped ulcer over the posterior aspect of the right os calcis. The center of the ulcer was deeply pitted, and its bed was made up of soft tissue that was similar to granulation and was described as having a "currant jelly-like" consistence (Fig. 1). The sinus tracts in the base of the ulcer extended down to the os calcis. There was a marked degree of induration about the lesion and the wound was tender when probed.

Examinations of the blood and urine were within normal limits, and the blood serologic findings were negative. Cultures of the draining sinus revealed *Pseudomonas aeruginosa* and a hemolytic *Staph. aureus*.

A ray examination showed no essential change in the appearance of the os calcis. The *Pseudomonas* infection was easily controlled with applications of 1 per cent acetic acid solution, after which penicillin was given intramuscularly (25,000 units every 3 hours) for 3 weeks. In early March because of continued improvement of the ulcerous lesion the patient was considered a candidate for skin grafting, but just before operation the lesion again broke down and drained a thin serous material from which a nonhemolytic staphy-

lococcus and a streptococcus were cultured. As the ulcerous area broke down repeatedly over a period of 6 weeks, guinea pig inoculation with samples of the serous drainage was carried out, and two biopsies of the sinus tract were forwarded to the Pathology Section.

The pathological report in mid-April was as follows:

The sections show loose granulation tissue densely infiltrated with round cells, plasma cells, polymorphonuclear leukocytes and fairly numerous giant cells. The polymorphonuclear leukocytes frequently form packed nodules surrounded by areas of necrosis. Closer examination reveals a number of oval or round bodies, which measure 10 and 20 microns in diameter, have thick refractile capsules and are filled with fine bodies resembling spores. The pathological diagnosis is coccidioid granuloma.

Subsequent coccidioidin skin tests and complement fixation studies confirmed the diagnosis and the fungi were plated out on appropriate culture material.

After consultation with Dr. C. E. Smith of Leland Stanford University, x-ray treatment was instituted but was given up

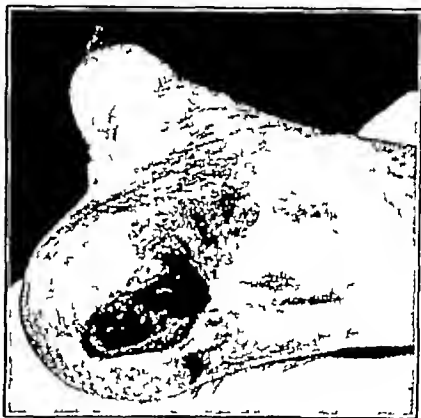


FIGURE 1 Photograph of Lesion

8 weeks later because of no change in the status of the lesion. In the interim streptomycin sensitivity tests in vitro proved this drug to be of no value.

During June the patient was given potassium iodide, which temporarily decreased the size of the ulcer, but this therapy was discarded 1 month later when the ulcer again broke down and a generalized typical "iodism" rash developed.

After an orthopedic conference it was decided that amputation was the procedure of choice, and the patient was sent to an amputation center where the right extremity was amputated below the knee joint, allowing for a functional stump. The amputation site was revised 2 months later. A follow-up examination 6 months later revealed that the stump had remained well healed. The patient's general condition was excellent at that time.

### SUMMARY

A case of localized coccidioid infection of the os calcis that did not respond to general and local therapy is presented. Amputation of the extremity



was followed by highly satisfactory wound healing without further dissemination

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## MEDICAL PROGRESS

### SYPHILIS (Concluded)

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#### *Syphilis in Pregnancy*

One of the most favorable situations for the use of penicillin in syphilis seems to be during pregnancy. The antibiotic appears to be especially effective during the gravid state, having almost a dramatic influence. It should certainly replace arsenotherapy without qualification in pregnancy with syphilis. Practically every report dealing with this phase of syphilis is an unqualified endorsement of the use of penicillin.

As in other phases of the disease, numerous schedules have been employed experimentally and the minimum treatment standards are beginning to be established. In general it is agreed that not less than 2,400,000 units of penicillin will be satisfactory<sup>63, 62</sup>. Results have shown that treatment of the mother as late as the seventh month of pregnancy is successful in obviating congenital disease, provided that the infant is viable. Penicillin thus has the advantage over chemotherapy in the treatment of syphilis in pregnancy since it may be given at any stage, even at termination of pregnancy, with at least a possibility of a syphilis-free infant, although early treatment is distinctly advisable. The usual follow-up study of the mother and infant can by no means be neglected. The incidence of Herxheimer reactions in pregnancy is high enough to necessitate relatively small doses during the first twenty-four hours, if the size of the penicillin injections is steadily increased, there is little or no likelihood of a Herxheimer reaction.

Some workers are using a minimum of 4,000,000 units of penicillin for syphilis in pregnancy<sup>63</sup>. With this amount it is believed that nonsyphilitic infants can be obtained regardless of the period of gestation in which penicillin therapy is started. It should be stressed that frequent observation is essential during the prenatal period to detect evidence of serologic or clinical relapse in the mother. Should this occur, a healthy child may still be obtained if retreatment is promptly instituted. A second course of therapy may also be necessary during pregnancy in a few patients who do not show satisfactory clinical or serologic response. Only a careful follow-up study, preferably with titrated serologic determinations, can tell whether a pregnant woman is making satisfactory progress after penicillin therapy during pregnancy. There is some belief that a syphilitic woman who has responded satisfactorily to penicillin therapy during pregnancy and delivered a normal infant need not be retreated during an ensuing pregnancy, if adequate follow-up observation is assured. This entails serologic studies and thorough examination at regular intervals after the original course of penicillin therapy and throughout each subsequent pregnancy. Should the woman then remain free of any evidence of syphilis, she might go through an ensuing pregnancy without treatment and produce a normal infant. If this fact proves to be true over a prolonged period and in a sufficient series of cases, it will have eliminated the necessity of treatment in each succeeding pregnancy in every woman who has ever had syphilis.

There is a report of the study of comparative effects of an aqueous solution of penicillin vs. POB

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in the treatment of the syphilitic pregnant woman<sup>44</sup> In this comparison only 2,400,000 units of aqueous penicillin was employed, as against 4,800,000 units of POB The over-all results were approximately equivalent in the two series, but one wonders whether equal dosage might have shown an advantage in the use of three-hourly aqueous solution Penicillin therapy for the pregnant woman should be at least that employed in the patient with early syphilis Although a total of 2,400,000 units may be sufficient to protect the fetus, the cure of the mother may require a higher dosage than this, and the 2,400,000-unit quantity should be regarded as an absolute minimum There is no obvious contra-indication to a larger dosage than this, and it should be unhesitatingly recommended Maximal rather than minimal therapy is most certainly desirable for both mother and infant There is some opinion that POB is less effective for symptomatic early syphilis in late pregnancy if the fetus is already infected In this situation better results should be more uniformly obtained by the use of an aqueous solution of penicillin with the woman hospitalized It is obvious that the risk of infection of the fetus would increase in proportion to the infectiousness of early disease in the mother, so that better results should be obtained among mothers with early latent syphilis and a still more satisfactory outcome when the woman has a late infection The same reduction of initial injections should apply whether the pregnant woman is treated with the aqueous solution of penicillin or POB On the first day 150,000 units of POB should be sufficient, this should be doubled on each of the two successive days, and thereafter 600,000 units daily may be continued for a week, providing a total dose of approximately 5,000,000 units

Another study compares the rapid treatment of syphilis in pregnancy by three different methods of approach arsenic and bismuth intensively administered in five to eight days, a penicillin-arsenic-bismuth combination and penicillin alone<sup>45</sup> The results were essentially satisfactory in all three groups, but it is obvious that the intensive arsenic and bismuth therapy should be abandoned and that the addition of arsenic to penicillin during pregnancy in syphilis is superfluous

### *Congenital Syphilis*

There are a number of communications regarding the treatment of all stages of congenital syphilis with penicillin In general the response has been good in earlier cases and satisfactory but much slower in late congenital disease This roughly parallels the course of the acquired form of the disease, as might be expected Interstitial keratitis has been notoriously poor in its response to penicillin, and nearly all observers have seen some cases of interstitial keratitis that were apparently aggravated by penicillin Even the combination of hyper-

pyrexia with penicillin has not provided anything like a uniformly satisfactory response in the treatment of interstitial keratitis

There seems to be uniformity of opinion that penicillin therapy in congenital syphilis is a safe and nontoxic method<sup>46</sup> Herxheimer reactions are as a rule not to be feared even in infants, and large initial doses are preferred<sup>47</sup> When clinical improvement has not been seen, the difficulty was usually attributed to anemia, debility or feeding problems The healing of all types of lesions was rapid in early congenital syphilis, but serologic response was in general slower than that observed in the acquired disease The doses employed have varied from 20,000 to 400,000 units per kilogram of body weight<sup>48</sup> Stokes<sup>49</sup> endorses the latter maximal figure Elapsed time of therapy ranges from seven and a half to fifteen days Negro children appear to have responded better than white<sup>50</sup> Clutton's joints and juvenile paresis have responded less satisfactorily but not so poorly as interstitial keratitis<sup>100</sup> The use of penicillin in osseous congenital syphilis appears to vary in accordance with the time of administration and the age of the patient<sup>101</sup> Doses of penicillin so far employed have temporarily accelerated healing of osseous syphilis only in infants treated during the first three months of life This acceleration occurs principally in osteochondritis and osteomyelitis, simultaneous improvement in periostitis is only of doubtful significance The latter seems to subside slowly after the first three months of life but does so in a more or less spontaneous fashion without much apparent influence from therapy Here again is an obvious indication for the earliest possible diagnosis and the institution of treatment during the first months of life if possible

Combined therapy of congenital syphilis with penicillin and arsenic and bismuth has also been advocated<sup>74</sup> One observer, however, seems to believe that penicillin is not the therapy of choice for congenital disease, regarding it merely as adjuvant therapy<sup>102</sup> The bulk of evidence is certainly against this opinion with the exception of those few types of involvement that have not so far responded too well, such as interstitial keratitis, articular disease, osseous syphilis and juvenile paresis Further study of methods and the various combinations of treatment may change this situation

It is not amiss perennially to call attention to the fact that syphilis in the newborn is prevented by proper therapy of the mother<sup>103</sup> Failure rates are reported as low as 1.6 per cent, even when penicillin therapy is administered as late as the thirty-second week of pregnancy, whereas the best of older methods failed in about 5 per cent of cases The one phase of syphilis that should be the most easily eliminated is congenital disease If all pregnant women were properly checked and treated as

indicated, this type of syphilis could be quickly stamped out

### *Neurosyphilis*

More reports have appeared in the literature regarding syphilis of the central nervous system than any other phase of the disease aside from early infections. The bulk of this material is related to therapy, and especially penicillin treatment.

A most interesting paper describes a study of the blood and spinal-fluid barrier and provides an explanation why positive Wassermann reactions occur in the cerebrospinal fluid of syphilitic infants, even though they show no clinical signs of neurosyphilis.<sup>105</sup> The method used was the administration of standard doses of sodium bromide by mouth, on the sixth day, the concentrations of bromide in the blood and in the spinal fluid were determined and compared, from which a permeability quotient was obtained. Normal and syphilitic infants and adults were examined in this fashion. In 8 newborn infants with moderately positive reactions of the spinal fluid, there were accompanying normal cell counts, total protein and colloidal gold values. These data, which could be obtained in adults who have been treated for neurosyphilis, usually indicate inactivity of a disease that has worn itself out, but this thesis cannot account for the findings in newborn infants. All 8 cases showed a high reagin titer in the blood serum, whereas the spinal fluid gave positive reactions with little or no dilution and the accompanying spinal-fluid tests were normal. This pattern may be explained by passive transfer of reagin from the blood into the spinal fluid.

In 4 infants who received antisymphilitic treatment, the spinal-fluid serologic studies showed an unusually rapid return to normal. This may be explained by assuming that the concentration of therapeutic agent in the cerebrospinal fluid is higher in children than in adults because of a highly permeable barrier between the blood and the spinal fluid. In 22 non-syphilitic infants the average permeability figure was significantly lower than the values listed for normal adults and closely approximated the quotients found for adults with neurosyphilis. This indicates that normal infants have an increased barrier permeability and that a positive cerebrospinal-fluid serologic finding in the absence of clinical evidence of the disease is not diagnostic of neurosyphilis and may be due merely to passive transfer of the reagin from blood to spinal fluid. Infants with no evidence of syphilis other than positive reactions to the serologic tests for syphilis should be followed without treatment to determine their status. Increasing reagin titers obviously indicate active disease and require treatment. This same procedure should be adopted in the therapy of infants with a positive spinal-fluid reaction, provided the cell count and total protein are within normal limits.

Asymptomatic neurosyphilis has been treated by several approaches employing the use of penicillin<sup>60, 74, 106, 107</sup>. From 4,000,000 to 10,000,000 units have been advocated both in single and in multiple courses. Penicillin exerts a favorable influence on the spinal-fluid changes in the following order: cell count, protein content, colloidal gold test and Wassermann reaction. The rapidity and the extent of the drug effect depend as a rule upon the severity of the spinal-fluid disorder before treatment and on the duration of the syphilitic infection. It is suggested that the reappearance of spinal-fluid abnormalities is an indication for re-treatment with fever and penicillin in combination.<sup>108</sup> Therapeutic malaria is still regarded by some observers as the most efficacious treatment for neurosyphilis.<sup>107</sup> The use of penicillin therapy alone in the treatment of neurosyphilis has not yet produced effects equal to those of malaria, but with lengthening experience it seems possible that results with penicillin will approach those of older routines.<sup>108</sup> The greatest effect on symptoms and signs has been observed in the mental aberration, inco-ordination, tremors and speech defects of paresis and in the lightning pains of tabes. There was no improvement in destructive lesions, and the advanced pareses were affected least of all. Another report, also dealing with the use of penicillin, predicates that the drug alone may approach or equal the effectiveness of fever therapy in neurosyphilis.<sup>109</sup> The subjective symptoms of tabes dorsalis were less influenced in this group of cases, but a trial of penicillin by itself was held justified in asymptomatic neurosyphilis, tabes dorsalis and meningovascular syphilis.

Combined hyperpyrexia and penicillin therapy have been used rather extensively, as might be expected. The two may be given concurrently or in succession. In a series of 210 cases there were 100 patients who had been followed for a year or more after treatment.<sup>110</sup> The basic course of therapy consisted of 3,000,000 units of penicillin in conjunction with a short course of fever therapy, but results indicated that this was not the optimum amount of treatment for late symptomatic neurosyphilis. Such findings are in accord with numerous others, who have advised maximum penicillin dosage as high as 10,000,000 units. A combination of penicillin with fever therapy is certainly to be recommended for symptomatic neurosyphilis, and many cases warrant the use of additional chemotherapy as well as penicillin and hyperpyrexia. The advent of penicillin has saved months and years of almost continuous treatment for many cases of neurosyphilis. It not only requires less time but also is safer and at least as efficacious as older methods of chemotherapy. It should certainly not be relied upon alone in cases of parenchymatous neurosyphilis, and a good many years must elapse before

more than tentative schedules of treatment can be relied upon

Army procedure recommends penicillin alone, with 9,000,000 units given over a period of twenty-two days, as an initial course for patients with asymptomatic neurosyphilis, acute syphilitic meningitis, diffuse meningovascular neurosyphilis, gumma of the brain or spinal cord and vascular neurosyphilis.<sup>111</sup> Penicillin in addition to fever therapy is stipulated for general paresis, taboparesis, primary optic atrophy, nerve deafness, syphilitic epilepsy and Erb's spinal spastic paraplegia. No further treatment with arsenic, bismuth or penicillin is given, but if after six months no clinical response is observed, retreatment with malaria and penicillin or with penicillin alone may be tried. A Veterans Administration bulletin on the management of neurosyphilis represents the latest combined opinion of a considerable number of authorities.<sup>112</sup> It is an outline of the most important considerations in the diagnosis and treatment of all types of neurosyphilis, including classification, diagnosis, treatment schedules, reactions, post-treatment observation and management of treatment failures and of relapses. It is a condensed but comprehensive review, and the treatment schedules advocated are in general agreement with the Army program and with other references cited above. The maximum course of penicillin is directed to consist of 9,000,000 units over a period of twenty-two and a half days. Fever produced by malaria is preferred to mechanically induced fever, and its combination with penicillin is advocated in all the visceral forms of neurosyphilis. It is stated that patients should be retreated if the cells and protein of the spinal fluid are definitely abnormal six months after treatment has been completed, or if the cell count and protein show a confirmed rising trend during the post-treatment examination period. When clinical response has been unsatisfactory, the patient may be retreated for this reason alone. Practically all patients who are retreated will receive malaria and penicillin unless individual circumstances preclude these measures.

A communication regarding the combined treatment of neurosyphilis with arsenic, bismuth and penicillin as compared with a group of patients receiving penicillin therapy alone, indicates slightly better results after the combined approach.<sup>113</sup> The difference was not statistically sufficient to warrant the additional risks of this particular combination as contrasted with the safety of penicillin alone. It might be suggested that the danger of arsenotherapy could be eliminated and the benefits of bismuth retained. Some syphilologists have for years believed that in a large percentage of neurosyphilis, bismuth therapy was at least equal in efficacy to trivalent arsenic. The authors of this current report observe that sufficient evidence is at hand to justify the treatment of asymptomatic

neurosyphilis with at least one course, and preferably several courses of penicillin, before resorting to fever therapy.

A pentavalent arsenical, Aldarsone, has been under study for several years in the treatment of neurosyphilis. It is said to have spirocheticidal power distinctly superior to that of tryparsamide and to be less toxic. The latest report concerns 54 patients who received over two thousand injections of Aldarsone.<sup>114</sup> The patients were treated with Aldarsone alone, in combination with other chemotherapy, or by Aldarsone combined with hyperpyrexia. The author concludes that Aldarsone is an arsenical of relatively high therapeutic efficiency and low toxicity that may be used with artificial fever and penicillin to improve the results in symptomatic neurosyphilis. The drug was well tolerated in nearly all cases, but untoward reactions were observed in 4. These consisted of herpes zoster, exfoliative dermatitis, nitritoid crisis and constriction of the visual fields. Although Aldarsone may be superior to tryparsamide in every respect, it is obvious that toxic reactions of considerable gravity may occur. Since penicillin acts so admirably as an improvement over all arsenotherapy, it seems only logical to reserve the Aldarsone as a secondary approach, when other methods of combined treatment have not produced satisfactory results.

Primary syphilitic optic atrophy has long been one of the most discouraging phases of this disease. Even when one eye is affected, it has often been impossible to stop progression and prevent involvement of the opposite eye. Chemotherapy has often apparently hastened the progress of blindness. Hyperpyrexia will sometimes suffice to arrest the optic atrophy, but some patients so treated have developed sudden and irremediable loss of vision. Relatively few cases have been treated since the advent of penicillin, but there is at least some encouragement offered thereby.<sup>115</sup> Stokes<sup>116</sup> advocates 10,000,000 units of penicillin combined with malaria therapy as the treatment of choice for optic atrophy. Vertigo is very rarely the only symptom in cases of central-nervous-system syphilis, but this phenomenon has been reported.<sup>117</sup> In the 2 cases described the presenting symptom resembled in all details that of labyrinthine vertigo. The significance of this was not recognized until neurologic examination and spinal-fluid studies had been done. The vertigo disappeared with antisyphilitic treatment, permitting the conclusion that this isolated symptom was probably due to syphilis.

A study of 300 cases of neurosyphilis treated with malaria indicates that *Plasmodium vivax* is a satisfactory inoculation for 90 per cent of white patients.<sup>117</sup> It was not an adequate method of inducing therapeutic fever for some persons who had previously had malaria, for Negroes or for those from the Mediterranean area and Puerto Rico. These subjects were inoculated with quartan malaria, and all but

1 of the white subjects treated by this form responded satisfactorily, all but 7 of 75 Negroes likewise had a therapeutic response to quartan malaria. In white patients who experience a moderate number of paroxysms after a primary vivax inoculation, but fail to attain a clinically adequate amount of fever, a heterologous strain of vivax may be successful. This work demonstrated the successful use of quartan malaria in those patients who are immune to *P. vivax*. In civilian practice, however, there are often difficulties in maintaining the two strains, unless there is a malaria center within reasonable distance to provide the material for inoculation, this approach is out of the question. The same students of susceptibility to malaria have emphasized the complications that may be encountered during therapeutic malaria.<sup>118</sup> Their report is composed of a separate communication derived from study of the same 300 patients. There were 22 cases of jaundice, all occurring during the malaria therapy. About 35 per cent of the patients received ten daily injections of Mapharsen during their convalescence, but no jaundice developed after the termination of malaria therapy. Twenty-one cases of edema were observed during the treatment. Albuminuria lasting for two days or longer was discovered in 48 of the 300 patients, and microscopical examination in 19 of these 48 cases showed varying degrees of hematuria. Four patients developed acute nephritis for which the malaria therapy was considered to be the direct etiologic factor. Thirteen patients developed respiratory difficulty unaccompanied by pneumonitis, 3 more showed roentgenographic evidence of the latter. Bronchial asthma was found to be markedly aggravated during malarial paroxysms. Exacerbations of tabetic crises and lightning pains were observed in 6 cases. Mental complications appeared in only 5 cases, which is a decidedly low incidence and undoubtedly due to the fact there were relatively few cases of advanced general paresis. It should be obvious that only qualified physicians with proper facilities should attempt to carry out any form of hyperpyrexia, whether malarial or induced by physical means. The material in the series of cases reported was all military personnel comprising comparatively young and healthy persons. A cross-section of neurosyphilis in the general population would reveal many more serious and advanced cases of neurosyphilis distributed among patients of lower vitality. Inmates of a mental institution would be deteriorated still further. It should be obvious that the incidence and severity of complications in civilian practice would therefore be grossly magnified and more dangerous than those reported in this current communication.

#### REACTIONS TO TREATMENT

Toxic reactions of considerable severity continue to be reported from the use of arsenotherapy.

Although penicillin treatment has been remarkably free from severe reactions, a few reports regarding such events have appeared.

#### *Lumbar-Puncture Reactions*

An interesting study of the physiologic and psychologic factors regarding lumbar-puncture reactions has been reported.<sup>119</sup> Of a series of 100 patients, punctures were done with a 16-gauge needle in 50 and with a 22-gauge needle in 50. Five times as many severe reactions occurred with the large needle, and the duration of symptoms was distinctly longer. The incidence of symptoms had no significant relation to the intelligence or emotional stability of the patients. Patients with normal moods seemed to suffer severer headaches than those who were depressed or elated. Hypochondriasis evidently predisposed to a slight increase in complications but did not raise the number of severe reactions. Suggestion appeared to be the psychologic factor of primary importance in the production of symptoms. Knowledge of ill effects in others did enhance anticipatory anxiety and exert a suggestive influence with a significant rise in the number of sequelae. The conclusion was reached that drainage was the most significant factor in the production of symptoms following lumbar puncture, outweighing by far the small contribution of anxiety, hypochondriasis and other emotional elements. The statement is occasionally made that constitutional inadequacy, increased suggestibility and emotional instability play a primary role in the etiology of lumbar-puncture reactions. The communication discussed above does not appear to bear out this opinion. Although many patients dread the procedure and have ill founded fears regarding the consequences, most syphilologists might well agree that the largest percentage of patients having post-puncture reactions are those who fail to follow instructions concerning rest and the avoidance of exertion. Hospitalization or bed rest may not be necessary in the majority of cases, but quiet and the omission of physical stress are of decided value.

#### *Penicillin Reactions*

In addition to the well known Herxheimer reaction, which may occur with penicillin as well as any other antisyphilitic agent, a number of reactions have been described.

The so-called "therapeutic paradox," in which a Herxheimer reaction may cause disastrous results, can usually be avoided by the administration of one fourth or one half of the usual amount as an initial dose and a subsequent increase with each injection. It is of decided importance to prevent the Herxheimer reaction in neurosyphilis, cardiovascular syphilis and all other late visceral disease. There is a distressing report of six severe Herxheimer

reactions following injections of such small doses as 1000 units of penicillin.<sup>120</sup> It is possible to avoid such reactions by the administration of a short course of bismuth prior to institution of penicillin therapy. This prophylactic measure serves just as well before penicillin treatment as when used prior to arsenotherapy and should be borne in mind for all cases of late syphilis. Another report concerns two Herxheimer-like reactions of neurologic character occurring in patients undergoing treatment of neurosyphilis.<sup>121</sup> These reactions were of such alarming proportions as to emphasize the advisability of using bismuth therapy in preparation for the penicillin treatment of neurosyphilis; it may well be considered for both symptomatic and asymptomatic disease.

A phenomenon observed by many is the occurrence of Herxheimer reactions in patients being treated by penicillin for infections other than syphilis.<sup>122</sup> The widespread and often indiscriminate use of penicillin may cause the involution of unrecognized lesions of syphilis and yet be insufficient to cure the disease. This not only can give rise to delayed sequelae and crippling complications but also may serve to sensitize the patient, leading to subsequent untoward reaction if penicillin is used for the treatment of syphilis or other infections. Regardless of the purpose of penicillin therapy, the occurrence of a febrile reaction of the Herxheimer type should provide sufficient cause for suspecting syphilis, even in the absence of serologic or other evidence. Moore<sup>40</sup> reports the incidence of Herxheimer reactions in early syphilis as being between 60 and 70 per cent of penicillin-treated cases.

A comprehensive review of the toxic reactions accompanying penicillin therapy divides them according to the role of penicillin as a direct toxin and primary irritant, as an antigen, as an excitant of therapeutic shock and through indirect action on pathologic processes.<sup>123</sup> Penicillin exerts a negligible action as a direct toxin or primary irritant except after its intrathecal use. With the latter method of administration the reactions may involve convulsions, meningismus or a shock-like state, apparently owing to direct irritative phenomena. There is divided opinion about whether intrathecal administration is warranted because of these reactions. They occur infrequently with the dosage employed intrathecally, but the value of this procedure is not sufficiently established to recommend it for more than experimental use. There is ample evidence that penicillin possesses antigenic and allergenic properties, although the reactions that result are less frequent with purified preparations. Sensitivity may be manifested as immediate or delayed reactions. Immediate reactions usually occur in known penicillin-sensitive patients, although a few persons appear to have a primary sensitivity without previous experience with the drug. Delayed

or acquired sensitization, which may be produced by repeated injections of penicillin, may be of short duration or can persist for years. The allergic symptoms following penicillin are usually benign and are of low incidence and transient nature. Urticarial or angioneurotic edema is by far the most frequent reaction and can usually be controlled by the administration of antihistaminic drugs. Fever and arthralgia may be more distressing features of these reactions and require considerable care. The urticarial phenomenon may occur within a few days after administration but has been observed as long as two to four weeks after termination of penicillin treatment. It is seldom that they persist for more than two weeks, but some have lasted for a month. A less common cutaneous reaction is the so-called "id" type of eruption, which has been observed not only accompanying all known methods of administration but also after topical application. It is often necessary to interrupt the penicillin therapy when this phenomenon appears. A case of agranulocytosis occurring during the course of penicillin therapy has been described.<sup>124</sup> The agranulocytosis occurred in association with a macular eruption, there was a rise in the white-cell count soon after penicillin had been discontinued, suggesting that the agranulocytosis was probably due to penicillin. Exfoliative dermatitis following penicillin therapy has also been described.<sup>125</sup> It was suggested that this reaction was due to some impurity in the penicillin used, since patch tests were positive with the brand of penicillin that had been administered but not with a different make of the drug.

In Romansky's<sup>22</sup> series of 4000 patients treated with POB there was a 5 per cent incidence of reactions, which in most cases consisted of urticarial or angioneurotic edema. The "id" type of eruption also occurred, appearing after each injection in a few patients and subsiding by the next day so that therapy was not interrupted. Occasional local reactions were also observed, usually after subcutaneous administration instead of intramuscular injection. This consists of a large patch of localized edema with erythema and a good deal of tenderness. The same peculiar local reaction has also followed the use of aqueous solutions of penicillin. The antihistaminic substances are not so useful with this phenomenon, which should be treated with the application of cold compresses, since hot packs are distinctly aggravating.

#### *Arsenical Reactions*

Reactions continue to be reported from the use of these drugs, especially after intensive arsenotherapy for syphilis. Among a group of 11 cases, only 1 occurred in the course of routine weekly injections of an arsenical preparation, the remainder appearing during intensive arsenotherapy.<sup>126</sup> Therapy with

2,3-dimercaptopropanol (BAL), pentnucleotide and liver extract, as well as blood transfusions in the severer cases, was followed by recovery in all cases. In another series of 500 cases of syphilis treated with moderate daily doses of Mapharsen over a twenty-day period, there were reactions of sufficient severity to interrupt therapy in 190 patients.<sup>127</sup> The reactions encountered in 24 of these cases required the permanent termination of therapy and included cerebral irritation, jaundice, toxic erythema, agranulocytosis, severe fever, hemorrhagic encephalitis and persistent albuminuria. Renal injury as a result of neoarsphenamine therapy is comparatively rare but has been reported.<sup>128</sup> Clinically, the manifestations were similar to those of nephrosis caused by bichloride of mercury and sulfonamide sensitivity, characterized by degeneration and necrosis of the cells lining the tubules.

The use of BAL in arsenical and other metallic poisonings has brought about a remarkable reduction in the severity of many cases of arsenical dermatitis. A study of 227 patients suggests that the proper administration of BAL will accelerate the recovery of patients with arsenical encephalitis, arsenical dermatitis, agranulocytosis or those who have received a massive overdose of Mapharsen.<sup>129</sup> The maximum dose of BAL that it is possible to administer intramuscularly in man at four-hour intervals is 4 mg per kilogram of body weight. Smaller doses on the order of 2.5 mg per kilogram of body weight are desirable to minimize local pain. With an average unit dose of from 2.5 to 3.0 mg of BAL per kilogram of body weight, it is recommended that from four to six injections be given daily for the first two days, with injections twice a day thereafter until recovery. There were 55 patients with arsenical encephalitis who received BAL, and the over-all mortality was 11 per cent. This is a remarkably low incidence of deaths. Among patients treated within the first few hours after the onset of symptoms, the recovery rate was distinctly higher than that in those in whom BAL therapy was delayed for a day or more. Among 88 patients with arsenical dermatitis, the average time for definite improvement in the patients with severe cases successfully treated was three days, thirteen days being required for from 75 to 90 per cent recovery. Of 11 patients with arsenical agranulocytosis only 1 died. In patients with postarsenical jaundice the BAL perhaps accelerates recovery in but a small proportion. In no case of this series was there a serious systemic toxic reaction due to the BAL, suggesting that the unit dosage and the number of injections could be increased in serious arsenical poisoning. Another communication reviews the history of the development of BAL with particular reference to arsenical dermatitis.<sup>130</sup> Undesirable side-effects of this drug are only minimal features if the dose is held to a figure of 2.5 to 3.0 mg per kilogram

of body weight, but beyond this point the incidence increases rapidly. The side-effects include nausea, vomiting, headache, burning sensation of the lips, mouth, throat and eyes, pain in the teeth, lacrimation and salivation, muscular aches, burning and tingling of the extremities, a feeling of constriction of the throat and chest and elevation of the systolic and diastolic blood pressure. These side-effects are usually at their maximum fifteen to twenty minutes after intramuscular injection of the BAL. All these side-effects, even those observed at the higher dosage levels, have so far been temporary. Barbiturates have been recommended as an antidote for the severest side-effects of BAL. This agent has proved of great practical value in preventing and in counteracting many other toxic effects of different arsenicals and of mercury. Its action against many other metallic and nonmetallic poisons is not proved and requires further study. It is most unfortunate that this exceedingly useful antidote to arsenic poisoning was not discovered about thirty years ago when arsenotherapy began to come into general use. It would have minimized many severe reactions and prevented a great many deaths.

\* \* \*

A few brief statements regarding penicillin might adequately conclude this progress report, so thoroughly has this remarkable antibiotic entrenched itself in the management of syphilis. Unfortunately, the disease has increased in the early post-war years, and a more potent antisiphilitic agent, as well as more effective control measures, is welcome. Although only rather general conclusions are as yet warranted with but a few years to study penicillin therapy for syphilis, giant strides have been taken. Penicillin is at least accepted as distinctly superior to any previously used antisiphilitic agent and is the least toxic. There is much to be learned regarding the antibiotic itself, as well as such factors as time-dose relation, effectiveness of the several penicillin species, role of impurities, prolongation of action and so forth.

The problems of resistance, relapse, reinfection, immunity and false-positive serologic reactions remain unaffected. There is at present no known true resistant strain of *Treponema pallidum* to counteract the effectiveness of penicillin, and it is to be hoped that even more effective commercial preparations will become available. No remarkably superior results have been obtained with penicillin as compared to the more effective chemotherapy regimes, but the relative freedom from reactions and saving in treatment time are invaluable attributes of penicillin. Its effectiveness in early syphilis is directly proportional to the speed of diagnosis and institution of therapy, although results in the secondary stage of syphilis still leave much to be desired. Beyond early disease, only neurosyphilis



has received much attention with the use of penicillin. Here its value is also great, but opinion is still divided regarding methods of approach. The ultimate results in all phases of syphilis cannot be determined for many years, and neurosyphilis may well be the last type deciphered.

In the pregnant syphilitic woman is seen perhaps the most amazing and convincingly demonstrated effectiveness of penicillin. This agent has proved its value in both the prevention and the cure of infection in the fetus when given late in pregnancy. There is even the remarkable prospect that subsequent pregnancies may not require retreatment.

Treatment programs for all stages of syphilis need much more study before optimal schedules can be outlined with general agreement. Combinations of penicillin and other antisyphilitic agents may finally prove the most desirable. Surety of diagnosis before institution of therapy and employment of fully adequate quantities of agents are of the same vital importance as in the past. Hospitalization of penicillin-treated patients is impractical for all but a few, and ambulatory-therapy plans are receiving due attention. It is to be hoped that the oil and wax preparations are at least a first step toward that end.

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**Correction** On page 2, in the first line of the next to the last paragraph, of the paper "Anticoagulant Treatment of Postoperative Venous Thrombosis and Pulmonary Embolism," by Drs. Evans and Dee, which appeared in the January 1 issue of the *Journal*, "0.6 gm." should be changed to read "0.06 gm."



## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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#### CASE 34051

##### PRESENTATION OF CASE

A sixty-six-year-old man, a millinery worker, entered the hospital for the first time complaining of shortness of breath.

One year before entry he first noted moderate exertional dyspnea. Ten days before entry he experienced an attack of epigastric discomfort, which was relieved somewhat by belching but which persisted and gradually became worse. One week before entry he experienced severe distressing dyspnea on retiring, with associated epigastric discomfort radiating over the chest. Subsequent to that episode he was anorexic and in varying degrees of distress, he could not lie down without severe dyspnea, and he developed a hacking cough productive of white sputum. The persistence of these symptoms led to admission to the hospital.

The past history included syphilis twenty years previously, apparently adequately treated, a blood test ten years later was allegedly negative. The patient denied a history and symptoms of diabetes, rheumatic fever or hypertension, and reported no previous dyspnea or chest pain.

Physical examination revealed a thin, dyspneic man with moderate distention of the neck veins. The heart was enlarged to the left by percussion, and the sounds were distant but regular, without friction rub or gallop rhythm. The pulmonic second sound was louder than the aortic second, and there was a Grade I systolic murmur heard in the left fifth interspace. Abdominal examination was negative.

The temperature was 99.4°F, the pulse 100, and the respirations 25. The blood pressure was 150 systolic, 90 diastolic.

Urinalysis was negative except for a +++ test for albumin and 2 to 4 red cells per high-power field and occasional granular casts in the sediment. The white-cell count varied from 11,000 on admission to 24,000 four days later. Repeated guaiac tests on the stools were negative. Blood chemical studies were not remarkable. An electrocardiogram demonstrated left bundle-branch block but no definite myocardial infarct.

On the third hospital day, while on the bedpan, the patient developed lower abdominal pain, which later radiated to the midepigastrium and resulted in moderate dyspnea. Nitroglycerin was given but gave no relief. On the next day he vomited some undigested food and later felt better. On the following day he was noted to have a distended abdomen with high-pitched peristalsis and reported complete obstipation since the onset of pain (forty-eight hours previously). A film of the abdomen at that time showed a nondilated, gas-filled large bowel and loops of small bowel, a glove specimen of the stool gave a ++ guaiac test. Enemas were nonproductive, and proctoscopy to 18 cm showed no mucosal abnormality. A Miller-Abbott tube was inserted, and the patient passed gas by rectum. A barium enema showed narrowing and spasm in the sigmoid, with diverticula, but was otherwise normal. The abdominal symptoms and distention improved, formed stools were passed by rectum, and the Miller-Abbott tube was removed.

On the twenty-second hospital day the patient had another episode of abdominal pain, with radiation to the right subscapular region, tenderness to palpation, most marked in the right upper quadrant, slight spasm in this region and diminished peristalsis. A questionable mass was palpated in the right upper quadrant on the following day. The serum amylase and van den Bergh determinations were normal. Tenderness later migrated to the right costovertebral angle, but x-ray films demonstrated clear renal and psoas shadows. On the thirty-first hospital day he suddenly developed a right hemiplegia and became disoriented and incoherent. A lumbar puncture showed clear, colorless fluid, with a spinal-fluid pressure equivalent to 145 mm of water and with a few fresh erythrocytes. Labored, wet, wheezing respirations were helped temporarily with Aminophylline. He became incontinent of feces and urine, Cheyne-Stokes respirations developed, and he died twenty-four hours later.

##### DIFFERENTIAL DIAGNOSIS

DR. DANA L. FARNSWORTH: May we see the x-ray films?

DR. STANLEY M. WYMAN: The film of the chest shows a slightly enlarged heart, without characteristic configuration. There is hazy density throughout both lung fields, most marked in the central portions and extending out to the central two thirds of the lung field. The extreme periphery in each lung is relatively clear. There is fluid in the left costophrenic angle in the pleural space.

A barium enema shows an area of narrowing and spasm in the midsigmoid with several diverticula. The examination was not continued throughout the colon. Subsequent films show the passage of a Miller-Abbott tube down into the jejunum. There is no marked distention or evidence of obstruction. One film shows several loops of gas-filled small

bowel, and these loops of small bowel are at the upper limits of normal in diameter. I can see no unusual soft-tissue masses or areas of calcification. The second barium enema demonstrates the same finding essentially. In addition, however, the proximal portion of the colon is fairly well visualized and shows no intrinsic disease. One film from the Grabam test shows dye in the gall bladder, which has a normal contour.

Dr FARNSWORTH: The presenting symptom of dyspnea suggests that the patient had heart disease, though this could have been due to pulmonary involvement alone. In chemical pneumonitis, particularly in beryllium poisoning, dyspnea may be the presenting and most disabling symptom. The occupation of the patient rules out this and probably most related possibilities. The acute episode ten days before entry is the one that focuses attention on the heart.

We are accustomed to thinking of severe substernal pain with or without radiation as the cardinal sign of a myocardial infarction. Actually this is the most important and frequent symptom, but dyspnea is probably the next most common symptom and may replace pain entirely. In many cases there may be a merging of the symptoms in such a manner that the patient interprets considerable dull pain as shortness of breath, and only close questioning will distinguish the two. The heart seems to have been beginning to decompensate because orthopnea developed. Shortness of breath is said to be more marked in the recumbent position than in the upright because blood flow through the heart is about 25 per cent greater in the former position; the lungs are more engorged, there is less room for breathing and free heart action with the diaphragm somewhat elevated, and the respiratory center is acted on directly by the stasis of venous blood. The balance in this case was very delicate, and the hacking cough and white sputum suggest pulmonary edema. The absence of hemoptysis makes pulmonary infarct less likely.

The past history is not of much help. The patient could readily have had hypertension for several years without being aware of it whether he had seen a doctor or not. I do not believe that syphilis had anything to do with the present clinical picture.

The physical examination throws further suspicion on the circulatory system—a fundamental cause of the trouble. The distended neck veins indicate backing up from the right auricle, the enlargement being consistent with a moderate hypertension of several years' standing, and the fact that the pulmonary second sound was greater than the aortic is consistent with beginning heart failure. The moderate degree of fever and the elevated white-cell count, indicating tissue destruction, make the possibility of a myocardial infarct even greater. It would be helpful for diagnostic purposes to have a typical electrocardiogram, but the presence of a

left bundle-branch block is to be taken quite seriously when considered in the light of the total clinical picture. The commonest cause of bundle-branch block is coronary atherosclerosis followed by greater or less degrees of coronary occlusion, whereas other causes, such as rheumatic myocarditis, syphilitic infection and diphtheria, do not seem to have been involved in this case.

The recrudescence of symptoms on the third hospital day may well have been an extension of the myocardial infarction, and it is also quite possible that thrombosis of some of the smaller mesenteric vessels developed, perhaps as a result of emboli from a mural thrombus. This latter complication may cause sudden abdominal pain, vomiting, sometimes diarrhea and shock. Distention usually follows. Occult blood in the stools is common, and according to Wangenstein\* about 5 per cent of such patients appear to have an abdominal tumor. If he did have mesenteric thrombosis in addition to further myocardial involvement, it was of relatively mild character each time he had a fresh attack. The house staff must have been wondering whether or not he had an acute pancreatitis, because of the serum amylase determination, or possibly they were concerned about disease of the gall bladder. Many patients with coronary-artery disease are operated on because they are thought to have an acute surgical abdominal condition, but it is just as bad, if not worse, to overlook a surgical abdomen on the assumption that the discomfort is due entirely to the heart condition.

A dissecting aneurysm must be considered, but this condition usually produces more severe back pain, together with radiation up or down, but particularly to the legs. The sudden development of a right hemiplegia with aphasia may have been due to embolism from a mural thrombus, but it is also consistent with the rupture of an arteriosclerotic vessel supplying the left internal capsule, probably one of the middle cerebral vessels. This was, of course, the immediate cause of death. The cerebrospinal-fluid findings are usually somewhat more abnormal than those in this case but not necessarily so. Whether hemorrhage or thrombosis occurred is uncertain, and either is possible here.

It would be possible to make two or more diagnoses to explain this man's illness and death, but I should prefer to make use of the principle often emphasized by Dr Cabot that one diagnosis should be made that will cover all the major symptoms. The entire picture should be explainable on the basis of hypertensive and arteriosclerotic heart disease, myocardial infarction in the left ventricle, the formation of a mural thrombus, with emboli to the mesenteric vessels and to one of the branches of the left middle cerebral artery (the so-called lenticulostratary group).

\*Wangenstein, O. H. Vascular obstruction. In Christopher F. A. Textbook of Surgery. Fourth edition. 1948 pp. Philadelphia: W. B. Saunders Co., 1945. P. 1057.

DR RICHARD J CLARK I should like to ask Dr Farnsworth how he feels about fluid in the left pleural cavity, in the absence of fluid in the right. Where does he think it comes from? Could it be caused by pulmonary infarction in the left lung, since most patients with congestive failure and hydrothorax have fluid on the right unless there is obliteration in the right cavity?

DR FARNSWORTH I think that an infarct is perfectly possible there

A PHYSICIAN Where would it be coming from? Would you not have to consider a thrombus on the right side?

DR FARNSWORTH With the history as incomplete as it is, I do not believe that I can absolutely state that this man did not have other peripheral circulatory difficulties before admission. I really cannot answer that question

A PHYSICIAN Then you have to make two diagnoses

DR FARNSWORTH Yes, if a pulmonary infarct is assumed

DR ARLIE V BOCK The case as outlined makes Dr Farnsworth's diagnosis quite easy, I think, but our problem while the patient was on the ward was somewhat more difficult. We felt that there was no doubt about the coronary occlusion and myocardial infarction, because of the history of pain and the presence of a certain amount of pulmonary edema. The troublesome feature was the persistence of pain in the left lower quadrant, the obvious distention of the descending and transverse colon suggesting partial obstruction in the region of the sigmoid. Too much attention was paid on our part to the suggestion of diverticulitis, of which there was no clinical evidence. The left lower quadrant was flabby and soft, with no mass or tenderness on pressure. Yet, practically throughout the hospital stay, distention of the colon was present. We could not believe that this was due to diverticulitis. We did not think at that time of the possibility of mesenteric thrombosis. The subsequent attacks of pain made us think of emboli, before the cerebral hemorrhage had occurred. Acute gall-bladder disease did not seem to be likely. The patient had exquisite tenderness, which appeared suddenly and again twenty-four hours later — the sort of thing that one associates with an embolus in the kidney, for example. I should be interested to know whether the pathologist found an adequate cause for the hemorrhage from the bowel, such as a mesenteric thrombosis

DR PAUL D WHITE Serial electrocardiograms might have been helpful. Only one is recorded

DR ISAAC TAYLOR Three were taken

DR TRACY B MALLORY Without significant change, I presume

DR TAYLOR Yes

A PHYSICIAN: Could the leukocytosis and fever fourteen days later have been due to myocardial infarcts?

DR WHITE Probably not. One would suspect some other condition or complication as a rule. I do not remember any case with leukocytosis and fever lasting fourteen days from infarct of the heart alone

DR BOCK. It is interesting that in this case, having suspected renal emboli, as I remember it, we did not find blood in the urine

#### CLINICAL DIAGNOSES

Cerebrovascular accident, probably occlusion of right and left anterior cerebral artery, (?) embolus from left ventricle  
Diverticulitis of sigmoid  
Cholecystitis

#### DR FARNSWORTH'S DIAGNOSES

Hypertensive and arteriosclerotic heart disease  
Myocardial infarct, left ventricle  
Emboli to mesenteric vessels, and to left middle cerebral artery

#### ANATOMICAL DIAGNOSES

*Coronary arteriosclerosis, with occlusion, left anterior descending*  
Myocardial infarction, old and new.  
Mural thrombus, left ventricle.  
Embolism, multiple, left internal carotid artery, splenic and renal vessels  
Infarcts, multiple, to brain, spleen and kidneys  
Chronic passive congestion.

#### PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed as the primary disease an occlusion of the descending branch of the left coronary artery, with a large area of infarction in the left ventricle. This infarction had occurred in at least two stages, possibly more. One was a very old fibrous scar, which was undoubtedly months old, then there were some fresh necrosis and some areas that seemed to be in between. On anatomic grounds I am not able to guess how many episodes of occlusion occurred. Overlying the area of infarction was a mural thrombus of the left ventricle, and from that a considerable shower of emboli developed. There were two infarcts of the spleen and multiple infarcts in both the right and the left kidneys. We found nothing else that would explain the abdominal symptoms. The mesenteric vessels were all patent, and there was no diverticulitis. In fact the diverticula were so small that we could not be certain of them at the time of autopsy. The terminal embolus was to the left internal carotid artery and produced extensive softening of the brain, predominantly of the left frontal lobe

DR WHITE What about the left lung base?

DR MALLORY There was 50 cc of fluid in each cavity, with no difference on either side, and no pulmonary emboli.

DR WHITE Was there any evidence of aortitis from the syphilis twenty years previously?

DR MALLORY None.

## CASE 34052

### PRESENTATION OF CASE

A seventy-three-year-old retired man was admitted to the hospital because of nausea and vomiting.

Three days before entry he developed nausea and vomiting of bile-stained food and liquid. On the following day he began to have pain and distention in the lower abdomen. These symptoms progressed. The vomitus became black. He was constipated, but an enema a few hours before admission relieved him of solid brown feces.

The past history was indefinite. The patient had been subject to asthma, hay fever and urticaria. He had four or five episodes of nausea and vomiting without distention in the past year, each lasting three or four days and subsiding spontaneously. There was a tendency to constipation, requiring laxatives for relief. A gastrointestinal series three months before entry demonstrated a duodenal diverticulum. There was no history of food intolerance, colic or acholic stools.

Physical examination revealed a well developed, well nourished man with dry skin and mucous membranes. The abdomen was markedly distended and diffusely tender, especially in the right lower quadrant. No peristalsis was heard. There were bilateral well healed scars from an operation for inguinal hernia. A rectal examination revealed an enlarged prostate. There were anal tags, and there was bloody fluid, similar to the gastric contents, about the anus. The liver was elevated above the rib margin. The diaphragm was elevated and moved well. Examination of the chest was negative.

The temperature was 102.6°F., the pulse 120, and the respirations 30. The blood pressure was 115 systolic, 80 diastolic.

The white-cell count was 6450, with 85 per cent neutrophils, including many immature forms. The hemoglobin was 18 gm., and the hematocrit was 50 per cent. There was 1700 cc of thick, fecal smelling grossly bloody gastric fluid aspirated, which gave a + guaiac reaction. The urine had a reaction of pH 5.5, with a specific gravity of 1.020, gave a + test for albumin and contained no acetone, only occasional red and white corpuscles were found in the sediment.

An electrocardiogram was normal. A plain film of the abdomen showed a massively dilated small bowel.

The patient's condition rapidly grew worse within one or two hours after admission to the Emergency Ward. Thirty minutes after entry he was in mild shock, with a blood pressure of 70 to 80 systolic, 40 diastolic, and a fast thready pulse. He was treated with penicillin, streptomycin, whole blood, "K" solution and dextrose in physiologic saline solution intravenously. A Miller-Abbott tube was passed. On the next day he was weaker and irrational. He passed into coma and died quietly.

### DIFFERENTIAL DIAGNOSIS

DR W. PHILIP GIDDINGS This is the story of a seventy-three-year-old man of allergic constitution, who except for four or five episodes of nausea and vomiting in the previous year, had apparently been in reasonably good health. He was admitted to the hospital after three days of nausea and vomiting with associated lower abdominal pain and distention. He was dehydrated and severely ill, and passed into clinical shock within thirty minutes of his arrival. Therapy did not avail, and he expired within twenty-four hours.

The physical findings were those of dehydration, complete ileus and gastrointestinal bleeding. There were fever and tachycardia of significant degree, and although these might be attributed solely to dehydration or to the effects of an ileus, I believe that in consideration of the silent abdomen and diffuse tenderness we must conclude that the patient had peritonitis.

The laboratory information disclosed that the heart and kidneys were probably normal. There was fairly marked hemoconcentration, as would be expected, and apparently no anemia. The white-cell response was struggling in the right direction, but apparently the toxemia prevented the elaboration of the large numbers of white cells that we should like to see. There was grossly bloody fluid in the stomach and rectum—the description of a + guaiac reaction in the presence of gross blood I take to have been an accidental discrepancy.

DR FRANCIS T. GEPHART The blood was grossly red but it showed a + guaiac reaction.

DR GIDDINGS The two findings are difficult to reconcile.

In the past history we learn of allergies, which I shall dismiss from further consideration. The tendency to constipation may or may not have had any bearing on the problem, there was nothing specific about it, and it could certainly have been incidental. I assume that a gastrointestinal series was done because of the recurrent nausea and vomiting, the finding of a duodenal diverticulum was probably incidental and, I should think, had nothing to do with the present illness.

The following points may give us some clues. Nausea and vomiting were the first symptoms. I infer that this episode somewhat resembled the previous attacks, and that the patient no doubt ex-

to the appeal represents a contribution on the part of every American to the welfare of distressed victims of war, especially children. In many communities the campaign is being co-ordinated with the annual drive of the local Community Chest. Co-operating agencies include United Service to China, American Relief for Czechoslovakia, American Aid to France, Greek War Relief, American Relief for Italy, United Lithuanian Relief Fund, Philippine War Relief of the United States, American Relief for Poland, Church World Service, American Friends Service Committee, War Relief Services and National Catholic Welfare Conference.

American Overseas Aid was organized at the suggestion of President Truman and in answer to increasing demands from community leaders for unification of aid to victims of war. An ancillary purpose is support of American foreign policy—a concrete demonstration of what America is willing to offer, as opposed to propaganda that would exploit the very wretchedness of the people concerned. Substantial relief will do much to reaffirm the value of the United Nations to those who may suspect that the benefits of alliance ceased with the end of military necessity.

But the appeal represents far more than an effort for ultimate political advantage. Americans, who responded willingly to the demands of wartime necessity, can be depended on to extend the hand of humanity to the less fortunate inhabitants of the earth who bore the brunt of the horrors and deprivation of war, the desperate needs of children in particular cannot fail to inspire a generous contribution. Doctors, who work ceaselessly for the amelioration of suffering, will not ignore the call to help relieve those who suffer most. The major reward is in the fine, unselfish giving itself.

#### MASSACHUSETTS MEMORIAL HOSPITALS

THE appointment has been announced of Dr. Philip D. Bonnet as superintendent of the Massachusetts Memorial Hospitals, to succeed Dr. Leverett S. Woodworth who has resigned to accept a position with the Veterans Administration.

Dr. Bonnet, who will assume his new duties on March 1, 1948, was born in Worcester and attended Wesleyan University, from which he graduated in

1932 and Harvard Medical School, graduating with the class of 1936. He has been associated with the Lankenau Hospital in Philadelphia as medical director, and since 1940 as director.

#### MASSACHUSETTS MEDICAL SOCIETY

##### NEW DIRECTORY AVAILABLE

The recently compiled directory of the officers and fellows of the Massachusetts Medical Society is now available at 8 Fenway, Boston 15, and will be forwarded to fellows of the Society on request.

##### DEATHS

**NORTHBRIDGE** — Robert J. Northridge, M.D., of West Upton, died on September 27. He was in his sixty-second year. Dr. Northridge received his degree from College of Physicians and Surgeons, Boston, in 1912. He was a former member of the Massachusetts Medical Society.

**VERDE** — Luigi P. Verde, M.D., of Dorchester, died recently. He was in his seventy-third year. Dr. Verde received his degree from Regia Università di Napoli Facoltà di Medicina e Chirurgia in 1900. He was a pioneer in administering the Schick test for diphtheria and was a former member of the Boston Health Department. His widow and three sons survive.

#### NEW HAMPSHIRE MEDICAL SOCIETY

##### DEATHS

**ALEXANDER** — Anson C. Alexander, M.D., of Penacook, died on January 3. He was in his ninety-third year. Dr. Alexander received his degree from Hahnemann Medical College and Hospital of Philadelphia in 1881. He was a member of the New England Gynecological Society. A daughter, a son, four grandchildren and three great-grandchildren survive.

**ROBINSON** — Richard W. Robinson, M.D., of Laconia, died on November 17. He was in his fifty-fifth year. Dr. Robinson received his degree from Yale University School of Medicine in 1920. He was a former president of the New Hampshire Medical Society and the New Hampshire Surgical Club and was a fellow of the American Medical Association and a member of the New England Section of the American Urological Association. His widow, three daughters, four sons and seven grandchildren survive.

#### A HUNDRED YEARS AGO

One of the remarkable books of the age, which deserves far more attention than it appears to receive, is from the pen of an English gentleman, Thomas Doubleday, Esq., on the true laws of population. He believes that a generous diet, maintained in a family, tends to its ultimate extinction; on the other hand, in new settlements, where a constant effort is demanded to procure the necessities of life, families without children are anomalies. Great prosperity, says Mr. Doubleday, and luxury in living, check increase, starvation, destitution, or a state bordering upon either, stimulate and encourage it. Excessively enriching the soil forces plants to run to straw, excessive eating, gluttony, and drunkenness, prevent reproduction of our species. China and Ireland are outstocked, simply

because there is never food enough, yet the former buoy up their hope with the comforting proverb, that *there never was a mouth without something to put into it* — The Worcester District Society has recently been favored with a legacy of six thousand dollars as a permanent fund, the income of which is appropriated to the purchase of books, apparatus, etc., and which, if it is judiciously managed, will produce, in another half century, a library of much importance to the Society — Dr Henry I Bowditch writes that the *Journal* was the first to announce the discovery of ether and has already recognized an improvement *Chloroform* is to all intents and purposes, *true chloric ether*. It is heavier than water, the taste is pleasant, it excites less cough, its odor does not infect the house of the individual, and a small quantity, averaging 100 drops, suffices to produce insensibility — Dr William R Lawrence reports that the Children's Infirmary in Boston has now been in operation for ten months 174 patients have been admitted, 57 above the age of 15 11 patients died, 2 from typhoid, 2 from ship fever, 1 with pneumonia, 1 with pleurisy, 1 with phthisis, 1 with dysentery, 2 from prostration, 1 from gangrene of the vulvae As to the treatment adopted, very little medicine has been administered, more has been due to the excellent care bestowed upon the children by the matron and the chief nurse, than to any prescriptions of the physician Among the out-door patients there have been a good number of cases of common tinea capitis The dietetic rules of the house have been somewhat rigid, and have been strictly enforced The usual beverage of the patients, until convalescent, has been iced water, and few have asked for anything else The bi-tartrate of potash has been given in a very few instances, when acid drinks were asked for The whole array of pleasant compound beverages has been discarded, and however difficult such a course might be in private practice, it has seemed here to have been attended with increased benefit to the patient — Two notices in commendation of Dr Meigs's Work on Females and their Diseases have appeared in this Journal We relished the style — a flowing, conversational freedom of thought and expression characterizing the whole, and giving even pretty grave parts an inviting aspect The fact could not be denied, as we thought, that the volume was well calculated to have an extensive circulation for Dr Meigs has discovered a lively, agreeable method of gaining the entire attention of the reader Dr Meigs may feel assured of continued popularity — The last arrival from Europe brings the melancholy intelligence of the death of the celebrated surgeon, Mr Robert Liston, at the age of 52 years — Shortly after the commencement of the lecture season now in progress, the Faculty of the Geneva College received an application, by letter, for the admission of a lady to the privileges of the Institution The Faculty

resolved to submit the letter to the class and the class adopted unanimously, resolutions expressing their willingness that the applicant should be received, pledging themselves to treat her with respectful consideration She was accordingly admitted, and has thus far attended the lectures in all the departments, as well as the surgical operations and dissections In so far as her presence in the lecture room has had any influence, it has been conducive to a more strict observance of decorum than is usual with medical classes It is understood that previously to her application to the Geneva College, she had applied to be received at the institutions of Philadelphia, New York City and Boston, but without success Geneva College will therefore be entitled to the distinction, meritorious or otherwise, of first practically exemplifying the experiment of opening the door of medical instruction to a female candidate for the medical profession Extracted from the *Boston Medical and Surgical Journal*, January 1848

R F

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The February schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows.

CLINIC	DATE	CLINIC CONSULTANT
Salem	February 2	Paul W. Hugenberger
Haverhill	February 4	William T. Green
Lowell	February 6	Albert H. Brewster
Greenfield	February 9	Charles L. Sturdevant
Gardner	February 10	Carter R. Rowe
Brockton	February 12	George W. Van Gorder
Fall River	February 16	David S. Gnee
Springfield	February 17	Garry de N. Hough Jr
Pittsfield	February 18	Frank A. Slowick
Worcester	February 20	John W. O'Neare
Hyannis	February 26	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments Patients are seen by appointment only

## NOTICES

### ANNOUNCEMENT

Dr James A. Hales announces that he has an office at the Faulkner Hospital

### MASSACHUSETTS TRUDEAU SOCIETY

A meeting of the Massachusetts Trudeau Society will be held at the Hotel Lafayette Boston on Tuesday, February 3 at 8 p.m. Drs. David Zacks and Albert M. Moloney will discuss Photo-Fluorography in Tuberculosis Case Finding Physicians and medical students are invited to attend

### SUFFOLK DISTRICT MEDICAL SOCIETY

A joint medico-legal meeting will be held by the Suffolk District Medical Society and the Boston Bar Association in Sanders Theater Harvard University Cambridge on February 5 at 8 p.m. The subject will be "Sex Offenders and the Law," with Dr. Harry C. Solomon as moderator Participants in the discussion will be Drs. A. Warren Stearns and George E. Gardner and Frederick T. Doyle first assistant district attorney of Suffolk County and Judge John J. Connelly of the Boston Juvenile Court

## JOSEPH H PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a m

### MEDICAL CONFERENCE PROGRAM

Wednesday, February 4—Observations on Amylase in Inhibitors Dr Joseph Volker  
Friday, February 6—The Use of Parasympatholytic Drugs in the Treatment of Bronchial Asthma Dr John Curry  
Wednesday, February 11—The Neurogenic Bladder Dr. Wyland Leadbetter  
Friday, February 13—Recent Advances in Our Knowledge of Blood Coagulation Dr Benjamin Alexander  
Wednesday, February 18—Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon  
Friday, February 20—Physiological and Pharmacological Factors on Gastric Secretion Dr Byron B Clark  
Wednesday, February 25—The Clinical Aspects of Surgery of the Extrahepatic Biliary Tract. Dr Norman J Wilson  
Friday, February 27—Clinicopathological Conference Drs Chester S Keefer and H E MacMahon

On Tuesday and Thursday mornings from 9 00 to 10 00, Dr S J Thannhauser will give medical clinics on hospital cases. On the second and fourth Friday afternoons of each month therapeutic conferences will be held from 2 00 to 4 00 with round-table discussion, Dr R P McCombs, moderator, Dr Merrill Sosman will conduct x-ray conferences from 4 00 to 6 00. On Saturday mornings from 9 00 to 10 00 clinics will be given by Dr William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12 00 to 1 00.

All exercises are open to the medical profession

## HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, February 10, at 8 15 p m

### PROGRAM

The Effect of a Vitamin A and Carotene Deficient Diet on Psoriasis Vulgaris Richard Hoffmann, M D  
Histochemical Identification of Cellular Enzymes Arnold Seligman, M D  
Recent Studies on Peritoneal Irrigation for Acute Renal Failure Howard Frank, M D  
Studies on the Clotting Defect in Hemophilia Benjamin Alexander, M D, and Andre De Vries, M D  
Studies on Blood Carbonic Anhydrase in Man Mark D Altschule, M D

Subsequent meetings will be held on March 9, April 13 and May 11

## NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, on Tuesday, February 10, at 8 00 p m. Dr Henry K Beecher's group will present a "Study of Sedatives"

### PROGRAM

An Appraisal of Amidone and Its Isomers as Analgesics Dr Jane E Denton  
The Influence of a Hypnotic (Barbiturate) on Psychomotor Performance. Dr Marcel Verzeano  
Problems of the Measurement of Sleep Dr Oliver H Straus

Physicians and medical students are invited to attend

## NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held at the Massachusetts General Hospital on Wednesday, February 11. This meeting is open only to members and invited guests

## TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet at the Boston Medical Library on Wednesday, February 25, at 8:00 p m. Dr Raymond Adams will speak on the subject "Vascular Diseases of the Nervous System"

## NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, February 25  
A detailed program will be announced at a later date

## AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology will hold practical examinations in Baltimore from May 20 to 25 and in Chicago from October 6 to 9. Written qualifying tests will be held annually, probably in January of each year. Applications for the January, 1949, written qualifying test must be filed with the Secretary before July 1, 1948.

## MISSISSIPPI VALLEY MEDICAL EDITORS' ASSOCIATION

Dr Morris Fishbein, editor of the *Journal of the American Medical Association*, will give an instructional course in medical writing at the annual meeting of the Mississippi Valley Medical Editors' Association, to be held in Springfield, Illinois, on September 29 during the annual meeting (September 29-October 1) of the Mississippi Valley Medical Society in that city. No registration fee will be charged to members of the Association.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING

#### THURSDAY, FEBRUARY 5

##### THURSDAY, FEBRUARY 5

12-00 m. Clinicopathological Conference Nurses Home, Allerton Hospital, Brookline.

##### FRIDAY, FEBRUARY 6

\*9 00-10 00 a m The Use of Parasympatholytic Drugs in the Treatment of Bronchial Asthma Dr John Curry Joseph H Pratt Diagnostic Hospital

\*10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital.

##### MONDAY, FEBRUARY 9

12 00 m Clinicopathological Conference Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge

\*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital

##### TUESDAY, FEBRUARY 10

\*12 15-1 15 p m. Clinicopathological Conference Peter Bent Brigham Hospital

8 00 p m New England Society of Anesthesiologists Massachusetts General Hospital

8 15 p m. Harvard Medical Society Beth Israel Hospital

##### WEDNESDAY, FEBRUARY 11

\*9 00-10 00 a m The Neurogenic Bladder Dr Wyland Leadbetter Joseph H Pratt Diagnostic Hospital

\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital

\*2 00-3 00 p m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital

\*Open to the medical profession

JANUARY-APRIL Thirteenth Postgraduate Seminar in Neurology and Psychiatry Metropolitan State Hospital Page 348, issue of August 28.

FEBRUARY 3 Massachusetts Trudeau Society Page 169

FEBRUARY 4-27 Joseph H. Pratt Diagnostic Hospital Medical Conference Program. Page 169

FEBRUARY 5 Suffolk District Medical Society Notice above.

FEBRUARY 6 American Board of Obstetrics and Gynecology Page 136, issue of January 1

FEBRUARY 8 National Conference on Medical Service. Page 136, issue of January 22

FEBRUARY 10 Harvard Medical Society Notice above.

FEBRUARY 10 New England Society of Anesthesiologists. Notice above.

FEBRUARY 11 New England Dermatological Society Notice above.

FEBRUARY 12 Shipping of Upper Femoral Epiphysis Dr John A. Reidy Pentucket Association of Physicians. 8 30 p m Haverhill

FEBRUARY 23-25 American Hospital Association Page 136, issue of January 22.

FEBRUARY 23-28 Postgraduate Assembly in Endocrinology Page 36, issue of January 1

FEBRUARY 25 Tufts Alpha Omega Alpha. Notice above.

FEBRUARY 25 New England Pediatric Society Notice above.

MARCH 9 New York Tuberculosis and Health Association Page 136, issue of January 22

MARCH 11 Fiftieth Anniversary of Cornell University Medical College. Page 136, issue of January 22

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston

(Notices concluded on page xvii)

## NOTICES (Concluded from page 170)

- APRIL 19-23 American College of Physicians Page 211 Issue of July 31  
 APRIL 29-30 and MAY 1-2 American Academy of Pediatrics Hotel Statler Buffalo New York  
 MAY 6-8 American Association for the Study of Cancer Page 211 Issue of July 31  
 MAY 16-23 International College of Surgeons Page 136 Issue of January 22  
 MAY 17-20 American Urological Association Hotel Statler Boston  
 MAY 18-22 American Association on Mental Deficiency Copley Plaza Hotel, Boston  
 MAY 20-25 American Board of Ophthalmology Page 170  
 MAY 25-27 Massachusetts Medical Society Annual Meeting Hotel Statler Boston  
 JULY 12-17 First International Pulmonary Conference Page 16 Issue of January 1  
 SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170  
 OCTOBER 6-9 American Board of Ophthalmology Page 10

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

- MARCH 9  
 MAY 11 Annual Meeting Hotel Walden  
 All other meetings will be held at the Franklin County Hospital

## MIDDLESEX EAST

- MARCH 24  
 MAY 12 Annual Meeting  
 All meetings will be held at the Bear Hill Golf Club

## NORFOLK

- FEBRUARY 24 Obstetric and Gynecologic Night  
 MARCH 23 Harvard Night

## PLYMOUTH

- FEBRUARY 19 Tott House Whitman  
 MARCH 18 Goddard Hospital Brockton  
 APRIL 15 State Farm Bridgewater  
 MAY 20 Lakeville Sanatorium Lakeville

## SUFFOLK

- FEBRUARY 5 Joint Medical Meeting with the Boston Bar Association

## WORCESTER

- FEBRUARY 11 Worcester State Hospital  
 MARCH 10 Memorial Hospital  
 APRIL 14 Hahnemann Hospital  
 MAY 12 Annual Meeting

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# The New England Journal of Medicine

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## MEDULLOBLASTOMA CEREBELLI\*

Diagnosis, Treatment and Survivals, with a Report of Fifty-Six Cases

FRANC D. INGRAHAM, M.D.,† ORVILLE T. BAILEY, M.D.,‡ AND WILEY F. BARKER, M.D.§

BOSTON

SINCE the first description of medulloblastoma cerebelli was published by Bailey and Cushing<sup>1</sup> in 1925, this rapidly growing tumor of the cerebellum has been recognized as occurring most often in children and leading to the abrupt onset of increased intracranial pressure and cerebellar dysfunction. Evidence has accumulated, however, that this typical syndrome is not always found in patients with medulloblastoma cerebelli and also that certain other tumors of the cerebellum give clinical symptoms indistinguishable from those of medulloblastoma. It is well known that medulloblastomas are much more successfully treated by irradiation than by radical extirpation. The place of surgery in the treatment of medulloblastomas, the amount of x-ray therapy desirable and the results to be expected are still open questions. We are therefore recording our experiences with medulloblastoma cerebelli with particular reference to the results obtained with various forms of treatment.

The series is composed of 56 patients from the following sources: patients seen at the Peter Bent Brigham Hospital since 1930, some of whom had originally been treated before that date in Dr. Cushing's clinic, and all the patients in the records of The Children's Hospital, many of whom were transferred to the Peter Bent Brigham Hospital for treatment before 1930. For this reason, some of these cases have already been reported elsewhere by other authors.<sup>1-12</sup> We have excluded from the series examples of the so-called "cerebral medulloblastoma," since it is not certain that they are identical pathologically with cerebellar medulloblastoma and since the clinical behavior of these two types of tumor is entirely different. Although medulloblastoma cerebelli is largely a tumor of

childhood, evidence that it occurs in adults more often than was previously thought is accumulating.<sup>12-14</sup> In all cases the diagnosis of medulloblastoma cerebelli in this series has been based on histologic identification, and sections of each tumor have been reviewed to exclude any not conforming to the present concept of this lesion. The specific anatomic locations are shown in Table 1. It is interesting to note that 15 of the 56 tumors did not occupy the classic midline position in or above the fourth ventricle.

Some authors<sup>6</sup> have believed that a difference exists between tumors arising in the midline, in the lateral cerebellar hemispheres and in the cerebello-pontine angle or in the pons itself. In our series there were no apparent differences in the natural history of the tumors in these sites. The only objective finding that varies in these locations is the average age of the patients, the ages were higher with pontile tumors than in those of the cerebellum (Table 1). However, the numbers involved are so small that the statistical significance of the difference in age is doubtful.

The distribution of all patients in the series according to age is in agreement with other reports. Twenty-four were in the second five years of life, and forty-two were in the first decade, but typical tumors were also seen in patients as old as thirty-seven and sixty-five years.

Distribution by sex was about equal, there were 31 males and 25 females.

Symptoms had been present on the average for slightly more than three months before the patient was brought to the hospital. The patient seen earliest after the onset of symptoms had noticed difficulty for only a week, and the longest pre-hospitalization period was twenty-four months. This is in agreement with the experience of many other clinics that the onset of symptoms in medulloblastoma is usually, but not always, rapid and that the symptoms follow a pattern of disturbed cerebellar function and increased intracranial pressure. It should be pointed out that medulloblastoma is

\*From the Neurological Institute, Children's Medical Center, the Surgical Service, Peter Bent Brigham Hospital, and the Departments of Surgery and Pathology, Harvard Medical School.

†Assistant professor of surgery, Harvard Medical School; neurosurgeon in-chief, Children's Hospital; chairman, Neurological Institute, Children's Medical Center.

‡Assistant professor of pathology, Harvard Medical School; neuropathologist, Children's Hospital; vice-chairman, Neurological Institute, Children's Medical Center.

§Formerly assistant resident in surgery, Peter Bent Brigham Hospital and Children's Hospital.

not the only tumor in the posterior fossa that causes abrupt onset of symptoms. Tumors that are much lower in malignancy and far more satisfactorily treated surgically sometimes give rise to clinical pictures indistinguishable from those due to medulloblastoma. For this reason, we believe it to be of the utmost importance to make a biopsy in each patient before roentgenotherapy is begun.<sup>11</sup>

Sixty explorations of the posterior fossa were carried out on 53 patients in this series. In 3 cases surgery was regarded as inadvisable in view of the condition of the patient. Biopsies were made in

TABLE 1 *Locations of Medulloblastoma Cerebelli in 56 Cases*

POSITION	NO. OF CASES	AVERAGE AGE yr
Midline	41	7.5
Pons and cerebellopontine angle	10	16.1
Cerebellar hemispheres	5	7.5

the course of these explorations. When larger portions of the tumor were accessible and could be extirpated without additional risk to the patient, this was done. In 3 patients it was necessary to expose medulloblastomas of the cerebellopontine angle through an occipital craniotomy after the suboccipital approach had failed to give adequate exposure. In 6 patients burr holes were made as procedures separate from a surgical approach to the tumor.

When the circulation of the cerebrospinal fluid was not re-established with certainty by removal of tumor or by freeing of adhesions, some further

TABLE 2 *Complications*

COMPLICATION	NO. OF CASES	NO. OF DEATHS
Metastases	19	2
Distant spinal or cerebral	10	
Local extension	9	
Acute gastrointestinal ulcerations	3	1
Postoperative intracranial hemorrhage	3	3
Wound infections	2	1
Bronehopneumonia	2	2

procedure was necessary to protect it. A tube was inserted for this purpose by the method of Torkildsen<sup>15</sup> in the course of seven of the sixty posterior-fossa explorations. The tube used in recent operations was made of polyethylene,<sup>16, 17</sup> which causes less tissue reaction than the rubber catheters formerly employed for the purpose. In 3 other patients third ventriculostomies were carried out as separate procedures, a right frontal approach being used. We prefer to use third ventriculostomies for older patients, but they have not been so successful in younger ones because the opening often closes

after a time. It is our impression that these operations have given the patients a maximum period of freedom from symptoms followed by a rapid downhill course in the terminal phases.

In all, seventy-two operations were performed on 53 patients, with an operative mortality of 32 per cent.\*

It has long been recognized that the medulloblastoma is more prone than any other glioma to

TABLE 3 *Clinical Symptoms Related to Metastases*

SYMPTOM	NO. OF PATIENTS
Somatic pain	7
Cord bladder	5
Complete paraplegia	2
Horner's syndrome	1

extend to the meninges and to produce secondary deposits within the cerebrospinal axis. The occurrence of metastases was demonstrated in 19 cases (Table 2). Of these, 10 showed distant spinal or cerebral seedings, the remaining 9 were local subarachnoid extensions. It is possible that the operative procedure is at times responsible for the dissemination of tumor particles. That this is not the only means of subarachnoid spread is shown by 2 cases in which metastatic implants were seen at the time of the first operation.

Not all these metastases caused definite symptoms, in 2 cases, however, a definite paraplegia was present. Cord bladder occurred in 5 cases, and 7 patients complained of severe pain in the distribution of spinal segments, which could be explained by no other cause (Table 3). One patient was even subjected to a laparotomy because of persistent right-lower-quadrant pain. This same

TABLE 4 *X-Ray Dosage and Survival Time*

X-RAY DOSAGE	NO. OF CASES	AVERAGE SYMPTOM-FREE INTERVAL	AVERAGE TOTAL SURVIVAL
Undetermined	6	mo 2.6	mo 7.4
None	17	0	0.5
150-2850	9	4.6	7.6
4500-9600	15	24.0	31.6
10800-30000	9	44.6	54.0

child's death was ultimately due in large measure to transection of the spinal cord by tumor.

Another complication was acute gastric ulceration, which occurred in 3 patients (Table 2). In only 1 of these cases were the perforation and extent of the resulting hemorrhage and peritonitis sufficient

\*Following Cushing's precepts,<sup>8</sup> we regarded any patient who died in the hospital during an admission in which an operation was performed as an operative death, although in some cases the cause of death was unassociated with the immediate operative procedure.

to be regarded as the cause of death. All 3 cases of postoperative intracranial hemorrhage were fatal. The only 2 cases of bronchopneumonia that were diagnosed at autopsy were terminal, but not agonal, and cannot be considered the sole cause of death. Of the 2 cases of wound infections, 1 was a fulminating streptococcal meningitis, which was fatal on the third postoperative day. The other was a slight infection of the superficial layers of the wound, which proceeded to heal well after only a brief delay.

Experience has shown that x-ray therapy is by far the most effective treatment for medulloblastoma cerebelli. Three patients in the series died before the institution of definitive treatment. Fourteen more patients were operated upon but did not receive roentgenotherapy in the early part of the series before modern therapeutic radiation was available. The majority (39 patients) were operated on and received therapeutic irradiation in addition. There were 9 patients still living on January 1, 1946—a case mortality of 84 per cent.

The survival of all patients is shown in Table 4, together with the amounts of roentgenotherapy received, and with an estimated "symptom-free" period of survival. These periods of survival are calculated from the date of the first hospital admission. The termination of the "symptom-free" period is based on purely subjective estimates from correspondence and outpatient records and has no objective criteria. It is the prolongation of this period, however, that is the chief goal toward which our therapeutic measures have been directed.

Six of the patients treated received undetermined amounts of roentgenotherapy, in 10 other cases completely accurate figures are not available, but figures representing minimum known dosages are used. In the remaining 23 patients, the dosages are known to be accurate.

Only 1 patient who received less than 4000 r of total therapy survived more than fourteen months, the average survival being slightly under eight months (Table 4).<sup>\*</sup> One of these patients was still living fourteen months after admission, but was in a nursing home for terminal care.

Fifteen patients received between 4000 and 10,000 r, with an average survival time of thirty-one and a half months. If the patient who survived for twenty-two years<sup>12</sup> is excluded, the average survival time falls to fourteen months. The average survival of all the patients who have died is seventeen months, the average "symptom-free" period of these same patients is slightly more than eleven months, excluding the patient who survived twenty-two years, this is lowered to nine months.

None of the patients who received more than 10,000 r is still alive, but the average survival period is fifty-four months, the least being seventeen

months and the greatest being slightly over twelve years. The "symptom-free" survival in this group is over forty-four months. It must be recognized, however, that although the larger dosages of irradiation may be assumed to be the cause of a longer survival, it is also true that only in those patients who lived for a fairly long time after admission could such large dosages be accumulated.

Several of these patients received unusually large total dosages over the course of several years, the biggest being approximately 30,000 r to the skull and spine over three and a half years. Some authors<sup>18</sup> have doubted the advisability of using such large dosages of therapeutic irradiation and have published reports of degenerative changes when dosages between 10,000 and 15,000 r had been used. In no cases in this series were any similar degenerative changes ascribable to roentgenotherapy specifically noted.

Systematic records of responses to x-ray therapy are not available on several of the patients with

TABLE 5 Causes of Death<sup>\*</sup>

CAUSE	No. of PATIENTS
Increased intracranial pressure	20
Increased pressure, local edema, shock	9
Postoperative hemorrhage	3
Meningitis	1
Accidental	1
Shock	1
Metastases	1
Undetermined	11

<sup>\*</sup>The number of living patients is 9.

<sup>†</sup>One patient also had an upper intestinal ulceration.

spinal metastases, 4 cases with adequate records demonstrated at least some response to therapy—in 1 case almost complete remission of pain for four years.

The clinical difficulties due to the irradiation were leukopenia, vomiting and acute cerebral edema. In 6 cases treatment was interrupted because of leukopenia (this occurred twice in 1 patient). Vomiting followed the irradiation in most patients, but in only 1 case was it of such magnitude as to require cessation of treatment. One patient died of cerebral edema after one treatment of 150 r. Autopsy showed a very edematous brain, with a marked pressure cone. The child also had an acute gastric ulcer, but this was not regarded as an important factor in the fatal outcome, since there was no evidence of perforation or bleeding from the ulcer at autopsy.

Tabulation in terms of survival periods without consideration of form of therapy reveals that there are 7 cases of three years' survival (12.5 per cent). Of these, only 3 went on to the five-year mark (5.4 per cent), 2 patients survived more than ten years (3.6 per cent). One of the last is still living

<sup>\*</sup>In calculations of these survivals only the patients who lived to receive any roentgenotherapy are included.

and in fairly good health twenty-two years after her original admission<sup>12</sup>.

Table 5 shows the causes of death in the entire series. Placed together are 20 fatal cases that can be ascribed almost entirely to one factor — increased intracranial pressure. Nine other deaths may be attributed to a combination of increased pressure, local edema, local trauma, local extension of the tumor and peripheral shock. In 11 cases no definite cause of death could be assigned, the patients having died outside the hospital.

Since the patients reported in this series have been treated by more than one neurosurgeon and over a long period, the forms of therapy used have varied considerably. On the basis of this experience our present choice of treatment has been exploration as soon as the diagnosis of a posterior-fossa tumor is made. Temporization with preliminary trials of roentgenotherapy does nothing but jeopardize the vision of children who have a benign cerebellar tumor<sup>11</sup>. If, at operation, it is possible to remove more than enough tissue for a biopsy, a larger portion of the tumor is resected, and a means for circulation of the cerebrospinal fluid is provided. As soon as the wound is healed, the patient is given an intensive course of roentgenotherapy, not only to the cerebellar area but also to the spine, in an attempt to destroy any metastatic seeding that may already be present. This first course of irradiation usually amounts to a total of 5000 r. It is followed in six months — sooner if the symptoms warrant it — by more irradiation through cerebellar portals. If there is evidence of spinal involvement, appropriate roentgenotherapy to the spinal portals is instituted. Re-exploration is indicated in the presence of obstruction to the circulation of cerebrospinal fluid, and an attempt to short-circuit the flow, by a tube as suggested by Torkildsen<sup>15</sup> in younger patients or by a third ventriculostomy in older patients.

#### SUMMARY

Fifty-six cases of medulloblastoma cerebelli are described, and the results obtained by various forms

of therapy evaluated. It is of great importance to establish histologic proof of the presence of medulloblastoma before roentgenotherapy is begun. Short-circuiting operations for the relief of increased intracranial pressure have been of considerable assistance in selected cases. Vigorous treatment of cerebellar medulloblastomas with irradiation is always indicated. Even if permanent cure can rarely be accomplished, it is possible to prolong a relatively "symptom-free" period of survival, which may then be followed by a brief downhill course.

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## THE PRACTICAL IMPORTANCE OF MODERN CONCEPTS OF PSYCHOSOMATIC RELATIONS\*

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THE term psychosomatic in its present-day usage serves commonly to designate a group of diseases with organic changes in which emotion is thought to play an important etiologic role. It is unfortunate, however, that there is a tendency to think of this approach as constituting still another specialty within the body of medicine. It would be far healthier if a broader concept could be adopted in which the attempt to study and describe both the physical and emotional aspects of illness could be viewed as a step toward the unification of all medical knowledge as it pertains to disease in a patient.

The recent investigations in this field are an approach toward incorporating into the structure of medical science what used to be known as the art of medicine. Everyone is familiar with the consummate skill of the experienced general practitioner, which combined a detailed personal knowledge of the patient, his past life and his family, with sound medical understanding as well as a great intuitive grasp of emotional problems and a warm friendly support. Striking therapeutic success and an excellent doctor-patient relation were often the result. However, these efforts could never be more than intuitive or empirical, nor could they be made predictable or manageable until they were subjected to careful psychiatric investigation.

To consider the patient as a person one must first accept the reality of emotional reactions. For example, one should not forget that nausea and vomiting may be caused entirely by strong emotions as well as by structural changes or by irritating substances in the stomach. Somewhat more difficult to visualize but now well established is the concept that emotion can eventually produce structural changes in the body. Once this is admitted a far broader view of the nature of disease must follow. It is vital that the patient be made to feel that he — and not his body alone — is the focal point of the doctor's interest.

From this it follows that psychogenic illness or any disturbance in which one cannot demonstrate organic change should no longer be considered as imaginary or even perhaps as consciously planned by the patient in an effort to deceive. Such an attitude defeats therapy before it begins. It brands the patient as a liar and denies the existence of his symptoms. One must make certain that the pa-

tient's feelings, his personal relationships, his life situation and his reaction to his environment are all subjected to the same painstaking scrutiny as his physical body and its symptoms. His emotions should be examined with the same objectivity as his organs, and here it is well to caution that moral judgment regarding behavior has no place in medical treatment. Irritating or annoying actions can be as much a part of a pathologic picture as organic disease and should receive from the doctor the same dispassionate appraisal, never unreasoning retaliation.

The first group of disorders of importance to the practicing physician are neuroses that manifest themselves by somatic disturbances, such as gastrointestinal, cardiovascular and skeletal symptoms. It has been estimated that from 30 to 50 per cent of all the patients seen in medical outpatient clinics are of this type.

It is highly important that such patients be handled properly from the outset. This implies that one take a careful medical history, which should include at least an attempt to outline the gross personality traits as they pertain to the illness. An adequate physical examination should follow, with special attention to the part of the body that is the seat of the complaint. Necessary laboratory work should be done when indicated.

At this point the physician can make or break the successful treatment of the case. If no significant organic changes are demonstrated, the patient should be so informed and should then be instructed, in the simplest words, concerning the mechanism of production of psychogenic symptoms. It is well not to use ambiguous or unfamiliar terminology and to be as definite and precise as possible, lest misapprehension arise. For example, many a patient becomes "heart conscious" and develops or perpetuates cardiac symptoms after injudicious remarks, too prolonged attention to examination without explanation or overemphasis upon nonsignificant findings such as murmurs and disturbances in rhythm. It is well always to minimize when possible, especially with these apprehensive patients. An evaluation of the patient's personality will give valuable clues regarding how much and what he can be told in such situations. All explanations should be clear and concise, and the patient should be encouraged to ask questions to allay any fears that he may have. Such care takes little extra time and results in very valuable therapeutic effects.

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If the disease is purely psychogenic, treatment should not be organic. Every neurotic person seeks to evade responsibility by falling back upon an organic diagnosis. It is more comfortable and more acceptable to explain symptoms as due to alien infections or other external causes than to accept personal responsibility as one must if one's own emotions, be they conscious or unconscious, are at fault. In this respect the experiences with such disorders during the war gave valuable information. Disability from acute somatic symptoms, which were due largely to emotional causes, was common in infantry soldiers under fire. When such men were asked for their explanation of the origin of their disturbances most were prone to blame external agents, few admitting that fear had played any part in making them ill. In this situation, an organic illness furnished an honorable way out in which fear had no part. A recognition of this chain of events and explanation of the psychologic aspects salvaged many useful soldiers for further action when it was accomplished soon after the onset. However, if the doctor made the error of accepting the patient's explanation of an organic external agent as the sole cause of his illness, he supported his rationalization and provided the neurotic process with the needed justification. All these men felt great guilt at leaving their buddies. The longer they were hospitalized, the greater the guilt and consequent need for further justification. Under such conditions recovery was greatly hampered and indeed often became impossible. Although such extreme pressures do not pertain to civilian patients, the underlying principles are the same, and the same precautions must be taken.

Unnecessary surgical procedures are especially harmful. In the presence of severe neurosis, the patient may often unconsciously seek such treatment in part as punishment for severe guilt feelings. Unless the indications are very clear-cut or an emergency exists, surgical procedures are best avoided in the presence of evidence of hysteria or other severe neurosis. Grave errors have been made in such situations with the newer operations to relieve pain. Such unwarranted interference not only has failed to give relief but also has too frequently led to repeated surgical measures that made eventual psychiatric care much more difficult.

There is no doubt that there is still a large group of patients in whom persistence of disability must be blamed on the injudicious medical management of psychogenic symptoms. Such cases are unnecessary and preventable. Usually, the treatment does not require specialized psychiatric knowledge. Adherence to the simple principles of considering the patient as a person, adequate examination, avoidance of unnecessary diagnostic procedures, simple explanation and reassurance usually suffices to alleviate or remove the symptoms and to restore

self-confidence. In severe cases, of course, specialized psychiatric treatment must be utilized.

Another important category of illness is made up of disorders in which recent studies have shown that emotional influences acting over longer or shorter periods result at first in disturbed physiology and eventually in structural change. Peptic ulcer is the simplest example. In this condition disturbed emotions lead to hypersecretion of gastric hydrochloric acid. When this has persisted long enough under certain conditions actual ulceration supervenes. Ulcerative colitis is another serious disorder in which emotional factors play an important role. In both these diseases dangerous complications and even death are not infrequent. Other disturbances in this group are the allergic illnesses such as asthma, hay fever and urticaria, certain skin diseases, such as eczema and neurodermatitis, migraine, possibly certain cases of epilepsy, hypertension and rheumatoid arthritis.

Addiction to alcohol and to drugs has long been considered a purely psychiatric disorder. Another addiction—namely, that to food,—which leads to simple exogenous obesity and which may result in the complications that are secondary to pathologic accumulations of fat, has been shown to have important psychologic aspects.<sup>1, 2</sup>

There seems to be emerging slowly a clearer understanding of the personality structure of persons who become ill in this way or who react with their bodies to certain emotional crises. These patients, usually unbeknown to themselves or others, appear to have remained or to have been pushed back to extraordinarily primitive and early stages of emotional behavior. They manifest an extreme degree of dependence upon certain key figures around them. This dependence on closer survey turns out to be so exaggerated that it suggests an almost symbiotic relationship. The loss of these key persons by death or by separation produces catastrophic helplessness and is often followed by organic illness. Lindemann<sup>3</sup> has reported that in 33 of 41 cases of ulcerative colitis, the disease began after the loss of important persons in the patient's life. The onset of rheumatoid arthritis after the death or illness of close relatives has frequently been reported in the past<sup>4, 5</sup> and has been observed in a small group of carefully studied patients.<sup>6</sup>

This extreme degree of insecurity and need for the support of others is manifested in various ways. It may be displayed openly as a childish, clinging, extremely demanding and grasping attitude with marked impatience and intolerance to any discomfort. On the other hand it may be completely hidden. In this event only the defense against the underlying weakness is seen in the form of an exaggerated false front of self-reliance and independence. The inadequacy of this defense becomes apparent when it collapses before any event that forces the patient into a dependent attitude. Such an event may be

the loss of economic status, the loss of key figures or separation from the family, a group or even a familiar environment. Loss of body substance or parts of the body, by injury or by operation, may also be a precipitating event. Apparently, many of these persons are extraordinarily dependent on the constant presence of outside help for the maintenance of security and psychologic integrity.

Coupled with this extreme degree of dependence is an exaggerated intensity of emotion. In consequence, these patients become extremely controlled outwardly and are usually considered to be cold and unfeeling. They fear any loss of control because it may result in an explosive and overwhelming outburst. It is as if they could express this intensity only through the channel of bodily symptoms.

Contact is difficult and they tend to live in isolation. Personal relations are difficult except on a superficial level. Their greatest fear is that of complete helplessness. Organic illness brings some recompense in that it is accompanied by the security secondary to attention and medical care. However so great is the fear of relying on others, paradoxically, that the patients may actually resist treatment. It is not infrequent to find this reaction in patients with rheumatoid arthritis, who persist in activity even though they know they should be in bed. Resistance to the effect of drugs—that is to being controlled by them—is another idiosyncrasy that is occasionally observed.

Eating is one primitive method of solving difficulties employed by these patients. For them, eating can assuage a sense of loss, of depression or of deprivation, and on the other hand it may serve to relieve anger or rage. At times it seems as if any discomfort can be relieved by this means. It is interesting that eating disturbances are not infrequent in such patients. Large fluctuations in weight, from obesity to pathologic weight loss, are common in the histories. Oral drug addiction is not rare, and one need recall only the very troublesome craving for tobacco that appears in certain patients with peptic ulcer, as well as the propensity for drug addiction in patients with rheumatoid arthritis even in the absence of a significant degree of pain.

These patients appear to have extremely loosely organized personalities. Their self-confidence is easily shattered by any deprivation or loss, whether of support from the outside or of a part of the body, by injury or operation. They are greatly dependent on outside help and react to insecurity with violent emotions. Responses are primitive and of total intensity. In this primitive stage such strong emotions are expressed by physiologic changes rather than by the more mature methods of physical activity, the outward expression of feeling or by verbalization.

What are the implications for treatment? To influence such patients, it is essential to establish con-

tact with them. This requires a very warm, friendly and giving type of approach, such as is usual and customary for the practitioner of medicine. It has been shown that therapeutic efforts may be defeated by the use of the passive psychiatric technique of exploration, which requires that the patient give a great deal of himself in words and ideas while receiving little in return.<sup>2</sup> Such efforts make demands on these patients of which they are incapable, and they are resisted with silence and hostility. They may result in actual exacerbation of bodily symptoms.

Every known therapeutic device must be utilized to demonstrate the doctor's interest and his willingness to help. This may be aided by attention to every detail of comfort and care from the medical, nursing and psychologic points of view.

It will be clear that such vulnerable persons will be suspicious and distrustful, and therefore it is vital that an attitude of extreme honesty be maintained at all times. If mistakes are made, they must be freely acknowledged. Strong support and reassurance are essential, and it is often necessary to infuse one's own optimism, confidence and strength of will into the patient. This he accepts by identification. The doctor may have to put himself temporarily into the role of the lost key figures or seek to manipulate the environment so that they are replaced.<sup>3</sup>

One must never try to push these patients too hard or too fast. Pressure is felt as rejection and hostility and either is strongly resented or produces exacerbation. One must avoid becoming annoyed by demanding and grasping attitudes. Often, these persons deliberately try one's patience by overt hostility. It is best to inquire into the reasons for such behavior, before retaliating. Many of them suspect that the entire world is hostile and cannot believe that anyone has any good intentions. The best results are obtained by gentle suggestion. One should attempt by every means to produce a therapeutic situation in which doctor and patient cooperate toward rehabilitation.

Restoration of maximal working efficiency should be a therapeutic goal equal to cure or alleviation of the disease itself. Emotional factors that may contribute to the dependency should be explored and removed whenever possible. Social service, by investigating and lightening the burden of family and environmental stresses, has much to offer. Occupational therapy should be so organized that it uses methods commensurate not only with the patient's physical ability but also with his intellectual and vocational aptitude. Under such conditions it can greatly assist rehabilitation. Vocational guidance, with retraining when indicated by the limitations of illness, deserves a larger place in organized medicine. Greater utilization of every facility available in the hospital and elaboration of



the concept of the therapeutic team should add greatly to the speed of rehabilitation

A word regarding the role of compensation and pension in disease is indicated. The justice and humanity of the principle of compensation for injury or illness sustained in industry or war are freely conceded, but a much greater understanding of the insidious and highly crippling effects of a continuing pension must become more widespread among the medical profession. Everyone has seen patients pushed into and maintained in chronic invalidism through the payment of weekly or monthly pensions. Especially if he is already insecure, the patient clings to his pension as his only lifeline, which although it is pitifully inadequate, protects him from complete helplessness. He is afraid to take steps toward independence even when there are no longer adequate physical reasons for disability because of the fundamental loss of self-confidence secondary to his illness. By the same token he cannot give up his only prop of compensation. Such behavior is neither conscious nor deliberate but represents a secondary neurotic dependency that is nurtured by the continued pension. From the point of view of rehabilitation, continuing compensation is not humane but hampers recovery. A review of present attitudes toward these practices is necessary, and lump-sum settlement offers one possibility for a solution.

Recent advances in the treatment of acute infectious disease have greatly decreased the dangers and economic loss from these illnesses. This requires that even greater attention be given to the large group of chronic and disabling diseases. If the patients are to be rehabilitated, the emotional relations that enter into the causation and treatment of their disease must receive much more study

and consideration, and this knowledge must become part of the thought and practice of every doctor.

In certain clinics in this country the psychiatric service has placed representatives in every outpatient clinic, surgical or medical.<sup>7</sup> Such close working together with every specialty has greatly furthered the understanding of the emotional aspects of illness in every special field and has made psychiatric knowledge much more available throughout the hospital. A wider application of such co-operation is to be welcomed.

It is likely that a new approach will have to be found to teach medical students these aspects of disease. Descriptive psychiatric teaching has its place, but it appears essential for every medical student to understand fully the psychologic development and the personality structure of normal as well as abnormal persons. It would be well if such teaching became an integral part of the entire medical curriculum.

Only complete consideration of all aspects of every patient and his illness — physical, emotional or environmental, and no matter in what special area of medicine — can eventually give an adequate understanding of the true mechanisms of disease and the most efficient and rational treatment.

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## THE CYTOLOGIC METHOD IN THE DIAGNOSIS OF CANCER\*

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TO MAKE a balanced judgment is always difficult. It is a human failing to see things either black or white and, often with insufficient evidence, to render an immediate and final decision either for or against. We shall describe a new test for cancer and present evidence of its value. It is not our contention that this new test should compete with biopsy or replace that method in the diagnosis of cancer. The electrocardiograph did not supersede the older methods of diagnosis in the detection of diseases of the heart. The eyes, the ears and the hand still remain the tried means of evaluating the cardiac state. Nevertheless, the electrocardiograph not infrequently reveals the presence of myocardial changes incapable of detection by the unaided senses, and it has become an essential aid in the interpretation of many cardiac conditions. The diagnosis of cancer by cytologic examination of body fluids bears a similar relation to diagnosis by the older methods. Not infallible, the new method nevertheless supplements the biopsy and in some cases gives information that the biopsy cannot give. Just as the electrocardiograph is now an indispensable aid in cardiology, so we consider the cytologic examination an essential complement to biopsy in the diagnosis of cancer.

Diagnosis by the cytologic method depends upon the fact that malignant tumors upon any free surface desquamate tumor cells into the surrounding medium. We are familiar with the continuous desquamation of normal cells, as evidenced by the constant presence of squamous cells in the vaginal secretion, the sputum and the urine. There is some evidence that the surface cells from malignant tumors desquamate even more rapidly than normal cells of similar origin.

For many years pleural and ascitic fluids have been examined for malignant cells, their presence depending upon the same property of desquamation. The method was first made applicable to other than metastatic tumors by Papanicolaou, who, in 1928, recognized cancer cells in the vaginal secretion of women with cancer of the uterus and on the basis of this observation published in 1941 the description of a new method of diagnosis of uterine cancer.<sup>1</sup> A detailed technic of the vaginal-smear method has

been described.<sup>2-4</sup> Briefly, a dry pipette with a capillary opening and capped by a rubber suction bulb, is introduced into the posterior vaginal fornix, the bulb is released, and the pipette withdrawn. The aspirated fluid is blown upon a previously marked glass slide, immediately fixed in equal parts of ether and 95 per cent alcohol, stained and examined for cancer cells. Criteria for the recognition of such cells is found in the articles to which reference has been made. Only after long experience may cancer cells be confidently distinguished from the many types of normal cells present in the vaginal secretion.

The value of this diagnostic method has been well established. Papanicolaou's<sup>1</sup> original report has been confirmed.<sup>4-6</sup> In a controlled study Hertig<sup>8</sup> obtained positive smears in 39 of 40 cases of carcinoma of the cervix and in 15 of 18 cases of carcinoma of the fundus. Eight positive and five negative smears were encountered in 13 cases of pre-invasive carcinoma of the cervix.

During the past five years in the Vincent Memorial Laboratory, 3710 cases have been studied by vaginal smear with a total diagnostic error of 2.8 per cent. Of 3327 cases without cancer, a mistaken positive diagnosis was made in 55. This represents an error (negative cases called positive) of 1.6 per cent.<sup>5</sup>

A recent publication suggests that many patients hitherto considered to have early cervical carcinoma, presenting but a short history of bleeding, or a minimal visible lesion may nevertheless be in an advanced stage of the disease, some even with metastases.<sup>10</sup> There is evidence that carcinoma of the cervix presents neither symptoms nor signs for as long as eight years after its inception.<sup>11-13</sup> In 47 cases of preinvasive carcinoma of the cervix reported by Pund and Auerbach<sup>10</sup> only 1 out of 4 patients had abnormal bleeding, and the cancer was not recognizable to inspection in a single case. If the gynecologist cannot visualize any suspicious area, he must take a biopsy specimen (or three or four specimens) hit or miss, 25 per cent of such biopsies fail to include epithelium,<sup>14</sup> and a larger number fail to include the malignant area.

In the diagnosis of very early carcinoma of the cervix, the vaginal smear is not infrequently more accurate than the biopsy.

The following and similar cases demonstrate that preinvasive carcinoma is often more successfully diagnosed by cytologic than by histologic examination.

Of 285 cases of cervical cancer 31 have been missed by smear. In 20 of 98 cases of endometrial carcinoma the smear was negative. It is evident that the vaginal smear is most accurate in cervical and less satisfactory in the diagnosis of fundus carcinoma.

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A 49-year-old woman, 3 years after the menopause, was given estrogens because of arthralgia. After 3 months of estrogen therapy, bleeding for 1 day occurred. The cervix was normal to inspection. A vaginal smear was positive. Biopsies taken from three areas in the cervix showed chronic cervicitis. A complete hysterectomy was done. The cervix was grossly normal. However, after the cervix had been sectioned, carcinoma was found in an area not over 0.5 mm in diameter.

A 42-year-old woman was admitted to the hospital because of a lump in the right breast, which proved to be benign. Pelvic examination showed a cervical erosion and leukoplakia. Cytologic examination of the vaginal secretion was positive for cancer. The diagnosis on a biopsy specimen was leukoplakia. A total hysterectomy was performed. Histologic examination disclosed preinvasive carcinoma of the cervix.

Seventeen cases of preinvasive carcinoma of the cervix, in which vaginal smears were positive in 15, have recently been reported.<sup>10</sup> Of thirteen biopsies taken from these 17 patients histologic diagnosis on the initial biopsy was positive in only 5. Four patients had had no symptom, a neoplastic lesion was unsuspected and was discovered only by routine vaginal smear.

### CANCER OF THE LUNG

Because pulmonary neoplasms desquamate into the bronchial secretion, the sputum has been studied for possible carcinoma of the lung. Dudgeon<sup>14</sup> was the first to introduce wet fixation as a diagnostic method. Gower,<sup>15</sup> Wandall<sup>16</sup> and others have obtained by this method a diagnostic accuracy of 60 to 80 per cent. Seed and Graham,<sup>17</sup> in our laboratory, have examined a single sputum specimen from each of 250 cases. A correct diagnosis for or against cancer was made in 73 per cent. In cases suspected of cancer the diagnostic error can be reduced by the examination of several specimens of sputum. It is important to note that in this series of 56 cases of primary pulmonary carcinoma, 7 cases were operable, sputums from 6 of these contained cancer cells.

### CANCER OF THE URINARY TRACT

A diagnosis of cancer of the urinary tract may be made by the examination of smears obtained from the urinary sediment. Our diagnostic accuracy has approximated 50 per cent. The following cases illustrate the value of the method.

I M, a 60-year-old patient, complained of hematuria and acute retention. Cancer cells were found in the urinary sediment. Cystoscopy showed cystitis, but no evidence of neoplasm. A biopsy taken at that time revealed only chronic inflammation. A total cystectomy was performed. Histologic examination disclosed cancer of the bladder, Grade II-B.

A S, a 79-year-old patient, had recurrent hematuria. Retrograde pyelograms showed a filling defect in the right kidney consistent with blood clot, but the possibility of tumor could not be excluded. The urinary sediment was positive for cancer. A nephrectomy was performed, cancer of the renal pelvis, Grade II-B, was found by the pathologist.

Until more statistical evidence is available, however, we believe that major operative procedures should not be undertaken on the basis of a positive

cytologic diagnosis of the urinary sediment unconfirmed by other examinations.

### GASTRIC CARCINOMA

The early detection of cancer of the stomach has so far proved an almost insoluble problem to the surgeon. Between 10 and 20 per cent of lesions that later prove malignant continue to be diagnosed as benign. Diagnosis of lesions that are grossly benign but histologically malignant is impossible either by x-ray examination or by gastroscopy, moreover, the surgeon at the operating table is frequently unable to decide whether a given lesion is cancer or benign ulcer. Pack and Livingston<sup>18</sup> state "If every patient with gastric cancer entered the best surgical clinic in the world, 95 per cent would remain uncured and approximately 90 per cent would be dead of the disease in 18 months." Without earlier diagnosis the salvage rate cannot be improved.

In 1946 Papanicolaou<sup>2</sup> reported 9 cases in which the aspirated gastric secretion was studied for cancer cells. Two of the patients had carcinoma. A cytologic diagnosis of cancer was made in both.

In the Vincent Memorial Laboratory gastric fluid in 50 cases has been examined. Twenty-four of these patients had cancer of the stomach. Cancer cells were recognized in the gastric secretion of 15. One case with a benign lesion was mistakenly called malignant. Cancer cells were found in 2 cases in which the excised stomach showed no gross evidence of neoplasia. Histologically both were diagnosed as preinvasive carcinoma. Of the 5 early cases of gastric carcinoma studied, cancer cells were found in the gastric fluid in 4. In 1 case, except for the cytologic report, cancer was totally unsuspected—preoperatively, at operation and on examination of the gross specimen. The application of cytologic examination to the diagnosis of early gastric cancer is now being investigated in the Vincent Memorial Laboratory.

### SUMMARY

The cytology of various body fluids has been studied as a means of cancer diagnosis. The value of the method for the diagnosis of uterine carcinoma has been established. In the detection of early cervical neoplasms, it is apparently more accurate than routine biopsy. Studies are in progress to determine the efficacy of cytologic examination in the diagnosis of cancer of the stomach, lung and urinary tract. In the early diagnosis of gastric carcinoma the new method may prove to be of great value.

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## RECENT THERAPEUTIC TRENDS IN ALLERGY\*

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DUSTON

TWO topics of current interest in allergy are considered in this study: the present status of histamine, with particular reference to the new antihistaminic drugs, and the role of inhalation therapy, including the aerosols.

It would be satisfactory to be able to report that recent advances in allergy have made clear an understanding of the fundamental characteristics of the allergic state. It is true that investigators are gradually learning more about the trigger mechanism that sets off the explosion, but unfortunately they are still ignorant of the nature of the charge with which the allergic gun is loaded. The chief constituent of this ammunition has long been supposed to be histamine. Study of this assumption has led to much investigative work over a period of years as well as to the development of several antihistaminic agents of clinical value. Feinberg<sup>1</sup> has reviewed this subject in an excellent article. A few points are worthy of emphasis, since they demonstrate the results of efforts to counteract the effects of this drug, whose role is presumed to be so important in the mechanism of the allergic reaction, particularly in the type associated with the immediate skin reaction and the production of edema and hyperemia.

As early as 1910, Dale and Laidlaw<sup>2</sup> called attention to the similarity of the action of histamine and the manifestations of anaphylactic shock in animals. In 1927 Best and his associates,<sup>3</sup> in demonstrating that histamine is normally present in many tissues, led the way to an explanation of its sources in the body. Variations in anaphylactic reactions in several species of animals were later considered to be due to varying concentrations of histamine in different organs.

In allergy in human beings, however, the importance of the role of histamine has not been so clearly

shown, but has been inferred more from certain similarities observed between anaphylaxis in animals and allergic reactions in man and by the fact that histamine administered to man produces some if not all of the phenomena observed in clinical allergy. Investigation of the systemic effects of histamine led Weiss and his co-workers<sup>4, 5</sup> to observe that vital capacity was decreased and that attacks of wheezing were frequently produced in patients with asthma after the administration of histamine. Daurehande et al.<sup>6</sup> further demonstrated the bronchoconstrictor properties of choline and histamine when employed as aerosols in human subjects. These observations were confirmed by Curry,<sup>7</sup> who pointed out that, whereas normal subjects showed no reduction in vital capacity after the administration of histamine, those with asthma did so if this drug was given by either the intramuscular or the intravenous route and, to a less extent, when it was administered under the tongue or by nebulization. Encouraging results have likewise been obtained by Curry<sup>8</sup> in a study of the effects of various drugs, including the antihistaminic agents, when he succeeded by their use in preventing or modifying changes in vital capacity after exposure to aerosolized extracts.

Treatment directed toward the histamine theory has taken several forms: immunization by treatment with histamine itself or histamine conjugate (hapamine), destruction by a ferment, such as histaminase, and inhibition or neutralization by the antihistaminic drugs.

Each of these methods of treatment has been tried. Desensitization by repeated injections of histamine has been widely attempted in allergic conditions in an effort to increase tolerance to this agent. The results of this type of therapy have been disappointing, and it is now concluded by most observers that such injections do not actually increase a subject's tolerance to histamine or significantly

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modify his own particular reaction to a given dose of this drug

Histamine azoprotein, a histamine conjugate, has also been employed on the grounds that it might more readily stimulate antibodies than histamine

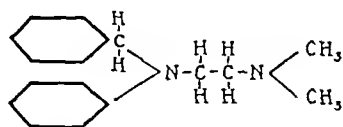


FIGURE 1 (*N'*-phenyl-*N'*-benzyl-*N*-dimethylethylenediamine) Antergan

itself, but this has also failed to produce consistent enthusiasm<sup>1</sup>

Histaminase provided what at first seemed a logical approach to a fundamental problem since this enzyme was proved capable of destroying histamine in many cases in vitro. In man, however, it did not produce comparable results so that even its dis-

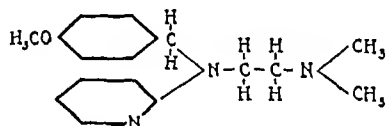


FIGURE 2 (*N*-*p*-methoxybenzyl-*N*-dimethylaminoethyl  $\alpha$  aminopyridine) Neoantergan

coverer, Best,<sup>9</sup> had to admit after ten years of trial that there was no physiologic basis on which to rest its clinical use

The development of the antihistaminic drugs constitutes the most recent and by far the most successful attack upon the effects of histamine. In contrast to attempted desensitization against histamine or

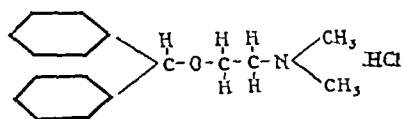


FIGURE 3 (*Beta*-Dimethylaminoethyl Benzohydril Ether Hydrochloride) Benadryl Hydrochloride

its destruction by enzymic action, these drugs produce their effect by neutralizing histamine by competitive chemical action. It may also be mentioned as a matter of contrast, that epinephrine, ephedrine and the other sympathomimetic drugs act in an entirely different manner—namely, by vasoconstriction. This distinction is of particular clinical importance, since it means that both types of drugs may be used together without mutual interference

After extensive trials with various compounds that had been shown to possess histamine-inhibiting properties, experimental observations with two antihistaminic drugs were reported in France. Halpern,<sup>10</sup> described antergan in 1942, and Bovet and his associates<sup>11</sup> neoantergan in 1946. Both drugs are effective. The latter, which is less toxic than antergan, shows particular promise.

Benadryl and Pyribenzamine, the new American histamine antagonists, have had more extensive clinical trial than the French compounds and are now generally accepted as of proved value in the treatment of certain increasingly clearly defined manifestations of allergy.

The structural formulas of these four compounds show their close chemical similarity (Fig 1-4).

Reports regarding the assets, liabilities and comparative merits and demerits of Benadryl and Pyn-

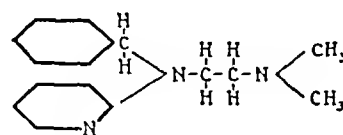


FIGURE 4 (*N'*-pyridyl-*N'*-benzyl-*N*-dimethylethylenediamine) Pyribenzamine

benzamine have flooded the literature. This paper is not concerned with summarizing these varying statistics but points out the conditions in which it is generally agreed that they are of value and to warn against their frequent side actions. Benadryl and Pyribenzamine are of greatest value in providing temporary relief in urticaria, angioedema and hay fever, in manifestations of serum disease, in the reactions due to penicillin or the sulfonamides and in the itching from atopic and contact dermatitis. They are less effective in perennial vasomotor rhinitis and even less so in asthma, particularly in cases of infectious or intrinsic etiology.

Side actions are frequent in both, the commonest of these being sedation and drowsiness. Vertigo, palpitation, nervousness, insomnia and gastric irritation appear less often. These occurrences sometimes become less marked after the first few doses, but they occasionally persist and necessitate discontinuance of the medication. The disadvantage of sedation may sometimes be converted to an asset when insomnia or anxiety complicates the picture, especially during the night or by day in cases of pruritus. Benzedrine may be of value in counteracting this drowsiness. There is a certain amount of selective response to these two antihistaminic agents in individual patients, both from the standpoint of therapeutic effect and in the appearance of side reactions.

An average dosage of 50 mg of either drug after meals and at bedtime is commonly sufficient to con-

tol symptoms, but this must be varied both in time and amount of administration in accordance with the patient's tolerance. The daily dose may be increased to 400 mg or over, in the absence of reactions, if necessary to obtain a clinical response.

It must be emphasized that these drugs do not immunize the patient, nor is their benefit more than a brief one, lasting but a few hours after each dose.<sup>12</sup> No evidence has been presented that they interfere with the mechanism of the production of immunity or that their prolonged and widespread administration is followed by remote toxic effects, but it is as yet too early for final judgment on these points.

The new antihistaminic agents are valuable adjuncts to the treatment of allergic disease, as epinephrine and ephedrine have been for some years. They do not minimize the importance of hyposensitization or of management by a carefully conceived and executed program, but when combined with other established methods of treatment, they do offer many allergic patients an increased chance of relief.

Inhalation therapy has made remarkable progress in recent years in the control of respiratory disease including bronchial asthma. Various therapeutic agents and methods have been introduced, particularly by Barach,<sup>13,14</sup> Segal<sup>15</sup> and others. The more notable advances have been the use of oxygen, mixtures of oxygen and helium and positive-pressure therapy, including the employment of therapeutic aerosols. Patients with severe asthma often respond to oxygen under normal pressure. If this fails, one should turn to oxygen or oxygen mixed with helium, preferably under positive pressure in both phases of respiration. The latter form of therapy can be administered with a Barach hood apparatus. If this is not obtainable, an O.E.M. mask, readily available to all physicians, may be used to supply positive pressure in the expiratory phase of respiration alone. Segal<sup>15</sup> recommends that positive-pressure therapy be carried on intermittently, for it may be tiring to the patient with uninterrupted administration, and he has further demonstrated that this form of therapy provides one of the most valuable methods in the treatment of severe bronchospasm.

Various therapeutic aerosols have been utilized for the management of certain phases of bronchial asthma. The bronchodilator drugs—epinephrine in a strength of 1:100 and vaponephrine and isuprel<sup>16</sup> (an isopropyl amino-ethanol)—have been found to be most effective for this purpose. A mixture of equal parts of 1 per cent Neo-Synephrin and any one of the above bronchodilators may occasionally prove of even greater value, since Neo-Synephrin, though a poor bronchodilator, is an effective broncho-vasoconstrictor.

The necessity for an efficient nebulizer must be emphasized. It is essential that the average mass diameter of the aerosolized particles be in the neighborhood of 1 to 3 microns to ensure their transit

into the lower respiratory passages and to prevent them from being deposited upon the mucous membranes of the upper respiratory tract. Most of the pioneer investigators in this field have found the vaponephrine nebulizer adequate for this purpose.<sup>16,17,18</sup>

Antibiotic aerosols, particularly penicillin, have more recently proved of benefit in many respiratory diseases, such as lung abscess, bronchiectasis, acute laryngotracheobronchial edema and purulent sinus disease.

Numerous reports in the recent literature, both favorable and unfavorable, have presented over-all results of penicillin therapy in bronchial asthma by the intramuscular, oral and aerosol routes.<sup>19-24</sup> On the whole, these have been disappointing except in cases in which there has been complicating purulent infection. When such a condition has been treated in the sinuses, favorable results in a small series of cases have been reported by Barach and his associates<sup>25,26</sup> with specially adapted equipment developed for the purpose. This consists of a negative-pressure sinus apparatus by which the nasal inhalation of penicillin aerosol is employed in conjunction with a scheme for interrupted negative pressure applied to the nasal passages. When this pressure returns to normal, penicillin is aspirated into the sinus cavities.

In the so-called "intrinsic cases" or in bacterial asthma, it might be thought that penicillin would often control the etiologic process and thereby arrest the disease, particularly when the drug can be concentrated locally in the pulmonary tissues, as penicillin aerosol can. In some cases, the penicillin-susceptible organisms can be eradicated in this way,<sup>21</sup> but the clinical course of the asthma is usually unaltered or is only temporarily improved. It should also be remembered that allergic reactions to penicillin, including the aerosol, are being encountered with increasing frequency, particularly in asthmatic subjects.<sup>27-29</sup>

Care must be exercised in the appraisal of the therapeutic efficacy of any procedure in bronchial asthma. The clinical picture may be modified by many factors other than the one under immediate consideration. Among these is the tendency for intrinsic asthma to exhibit seasonal fluctuations, improving in warm weather and becoming worse with recurrent infections in the winter. Hospitalization itself, with its change of environment, provides multiple factors of a therapeutic nature, both medicinal and psychologic, that often bring about a remission, as does the careful control of previously unrecognized extrinsic allergens or of structural abnormalities. Penicillin should therefore be considered as a therapeutic agent for the treatment of clear-cut infectious processes and not as a routine procedure in the therapy of bronchial asthma.

Brief mention should be made of promising results obtained after the recent employment of aero-

sols for the purpose of testing asthmatic patients who have failed to react to suspected pollens by routine skin tests. Lowell and Schiller<sup>30</sup> have exposed such patients to the inhalation of various pollen extracts, recording the resulting effect upon their vital capacities. These authors have been able to demonstrate that substances that produce a fall in vital capacity are of clinical significance as judged by the histories and by the production of mild asthma characteristic of the seasonal attacks.

### SUMMARY

The modern concepts of the possible role of histamine in the mechanism of the allergic reaction are discussed. It is pointed out that treatment with histamine or with histamine azoprotein does not give adequate clinical evidence of increased human tolerance to histamine and that the enzyme histaminase is not capable of destroying histamine in vivo. The new antihistaminic drugs, which apparently operate by competing with the liberated histamine in their attachment to the receptor cell, have been more successful in treatment. The temporary nature of their action, their advantages and their disadvantages are reviewed.

Recent advances in inhalation therapy for asthma are described, including the use of therapeutic gases, both with and without positive pressure, and the administration of various therapeutic aerosols. A new method is pointed out by which aerosolization may be utilized for further investigation of the action of drugs of potential value in allergy and for the study of cases of asthma of inhalant origin refractory to better known methods of testing. The limitations of penicillin in the treatment of chronic asthma are set forth.

Allergic symptoms are potentially recurrent and may appear in varying forms dependent upon the changing location of the shock organ. They are the manifestations of a chronic, constitutional inherited disorder, the exact nature of which is still unknown. No one method of therapy or agent that will afford more than temporary relief once these symptoms have appeared has yet been discovered, nor can it be instrumental in controlling the precipitating factors that lead to the appearance of manifestations recognized as allergic disease. For this reason it is strongly recommended that the new drugs and procedures outlined above, as well as all others that have been introduced to date, be employed, not as isolated methods of therapy but as supplementary aids to already well established principles of treatment. There is as yet no short cut

and no substitute for sound allergic management, which includes prolonged observation and education of the patient in conjunction with elimination and desensitization when these procedures are indicated.

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SEPTICEMIA DUE TO *PROTEUS VULGARIS*\*

## Review of the Literature and Report of a Case Cured by Streptomycin

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THE term *Proteus vulgaris* (*Bacillus proteus*) refers to a number of different species of a gram-negative, actively motile rod form originally described in 1895.<sup>1</sup> These organisms characteristically exhibit the "swarming" phenomenon in colonies on agar. They are widely distributed in contaminated soil and sewage and are found on the skin, in the urine and in the mouth.<sup>2</sup>

The *Proteus* organism was at first thought to be nonpathogenic, but Larson and Bell<sup>3</sup> established its pathogenicity for rabbits, rats and guinea pigs in 1915. It has since been implicated in a large number of pathologic states, though its usual status is that of a nonpathogen and it is found in a high percentage of normal stools.<sup>4</sup>

*Proteus* septicemia is a relatively rare condition. Cragg<sup>5</sup> stated in 1941 that 13 cases had been recorded in the literature. McKee<sup>6</sup> reviewed *P. vulgaris* infections in 1944 and found 23 cases of septicemia produced by foci of infection other than the genitourinary tract. Data on 52 reported cases<sup>5-13</sup> are presented below, together with a report of a case cured by streptomycin therapy.

## AGE, SEX AND SOURCE

The youngest reported case was in a nine-day-old infant,<sup>9</sup> and the oldest in a seventy-five-year-old man.<sup>10</sup> Between these two extremes, the cases were distributed generally among all decades, with the exception that a larger proportion of cases were in the third decade. Of the patients who were under forty, roughly four fifths had middle-ear infection, and of those over forty, about four fifths had primary genitourinary-tract disease.

About 75 per cent of the patients were male and 25 per cent female.

Of 47 cases in which the source of the septicemia was established, 21, or 44.7 per cent, originated in the ear, nose or throat, 22, or 46.8 per cent, originated in the genitourinary tract, and 4, or 8.5 per cent, derived from miscellaneous foci.

Among the cases associated with genitourinary-tract infection, 7 followed directly the use of instrumentation (catheterization or cystoscopy) and 8 were caused by major operations of the genitourinary tract—5 after prostatectomy and 1 each after suprapubic cystostomy, nephrostomy and nephrolithotomy. Two cases were associated with pyelonephritis,

and 1 each with cystitis, pyelitis, renal tuberculosis, carcinoma of the bladder and cord bladder.

The source of infection in the 21 cases involving the ear, nose and throat was the middle ear in 18, the tonsils in 2 and a questionable pharyngeal ulcer in 1 case.

The remaining 4 cases were associated with a suppurative ovarian cyst, a lung abscess, a war wound and meningitis in a nine-day-old infant.

## PATHOLOGY

Few detailed pathological reports are available. Characteristically, all infected areas exhibited a foul-smelling, green or brownish-green pus. Lung abscesses containing the typical foul pus were found in 6 of 9 cases in which autopsy findings were reported. Isolated findings included septic thrombosis of the inferior vena cava, lateral sinus thrombosis, thrombophlebitis of the renal veins, congestion of the spleen, brain abscess, purulent meningitis from *P. vulgaris*, pyelonephritis, osteomyelitis and chronic otitis media. The microscopical pathology was not distinctive, an outpouring of polymorphonuclear leukocytes being most characteristic.

## CLINICAL PICTURE

In most cases, the patients appeared acutely ill and ran a high, spiking fever with chills and a septic course. Occasionally a typhoid type of fever curve was seen, and some cases diagnosed as typhoid fever came to post-mortem examination. Anemia was present in some cases, and leukocytosis in almost all. White-cell counts ranged from 8700 to 35,000, with an average level of 12,000 to 16,000. The differential count showed from 70 to 84 per cent neutrophils.

When recovery took place, the illness was usually of many weeks' duration. In cases in which operative procedures preceded infection, recovery, when it occurred, was more rapid.

Division of the cases into two groups based on the source of the infection—the ear and the genitourinary tract—establishes the symptomatology associated with most cases. In those deriving from the ear, a history of chronic otitis was almost invariable, and associated pain and discharge were present. In those related to the genitourinary tract, the history of previous operative procedures was present in 15 of 22 cases, and typical symptoms of urinary-tract disease with concomitant chills and fever were noted.

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### PROGNOSIS

In 48 cases in which the subsequent course was described, 31 patients, or 64.6 per cent, died, and 17 patients, or 35.4 per cent, recovered. The prognosis was far better in the cases deriving from the genitourinary tract than in those deriving from the ear, nose and throat. In the former group, the mortality was 36.8 per cent, whereas in the latter group it was 80.1 per cent.

### DIAGNOSIS

The diagnosis can be established only by obtaining a positive blood culture for *P. vulgaris*. When positive blood cultures are obtained, investigation of the two main foci of infection is imperative.

### CASE REPORT

A 44-year-old man entered the hospital with a chief complaint of chills and fever of 3 weeks' duration.

He had previously been admitted to the hospital seven times since 1932 for recurrent renal calculi, but on each occasion he had been able to pass the stones without operative intervention. The last previous admission had occurred 5 months before the present illness. At that time, the patient passed eight small calculi and one large calculus. After cystoscopy, he developed a shaking chill and fever, and during the week following discharge from the hospital, he had three episodes of chills and fever. One month after discharge, he began to notice moderate shortness of breath on exertion and at that time was told that he had a heart murmur. Three weeks before the present admission, he began to have recurrent episodes of shaking chills and fever at about 9 o'clock each evening. He was placed on sulfonamides and remained afebrile for a few days, only to have a recurrence of the chills and fever. Sulfonamides were discontinued, and penicillin therapy initiated, but the penicillin failed to influence the course. The patient was then hospitalized.

Physical examination revealed the presence of marked generalized pallor, slight cardiac enlargement, and a loud, harsh, apical systolic murmur heard throughout systole and masking the first sound. No other positive physical findings of note were observed.

On the afternoon of admission, the temperature was normal, but it rose to 103°F in the evening, after a shaking chill.

Examination of the blood showed a hemoglobin of 9 gm and a white-cell count of 10,000 to 12,000, with 74 per cent neutrophils, 20 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. The hematocrit was 28 per cent, and the corrected sedimentation rate 30 mm in 1 hour (Wintrobe method). The blood sugar was 109 mg, and the blood urea nitrogen 22.1 mg per 100 cc. The total protein was 7.5 gm per 100 cc, with an albumin of 4.1 gm and a globulin of 3.4 gm. The icteric index was 6.0, the blood calcium was 10.6 mg and the phosphorus 3.5 mg per 100 cc, and the alkaline phosphatase 4.5 units per 100 cc. The urine had a specific gravity of 1.024 and contained a trace of albumin, with 10 white cells per high-power field in the sediment and a negative Sulkowitch test.

Blood cultures were taken, and on the 6th day after admission, a pure culture of *P. vulgaris* (15 colonies per cubic centimeter) was reported. At the same time, a pure culture was found in the urine. Positive blood cultures were again obtained during the next 2 days, and the patient was then placed on streptomycin, 0.3 gm every 3 hours. He remained on streptomycin for 10 days, receiving a total of 25 gm. No positive blood or urine cultures were obtained after the initiation of streptomycin therapy. After the 1st day of treatment, the patient had no more chills, and the temperature never went above 101°F. After a week of normal temperature, he was discharged and has remained well ever since.

### DISCUSSION

From the review of the literature presented above, it is apparent that *Proteus* septicemia formerly had

a high mortality. That the prognosis was worse in cases associated with disease of the ear, nose and throat was probably due to the long-standing and deep-seated infection that led up to the septicemia.

Therapy, until the advent of streptomycin, was varied and not demonstrably the direct cause of cure. Surgery was utilized in 9 patients. Of 6 patients on whom mastoidectomy was performed, all died. Two of 3 patients on whom nephrectomy was performed survived. Recovery followed bacteriophage in 1 case<sup>40</sup> and vaccine in 2 cases,<sup>10, 18</sup> and sodium ricinoleate therapy was followed by recovery in 1 case.<sup>40</sup> Sulfonamides were used in 3 cases, 2 of the patients died,<sup>43, 44</sup> and 1 survived.<sup>6</sup>

In the National Research Council Report on streptomycin<sup>46</sup> 5 cases successfully treated with streptomycin were noted. No data were obtainable in these cases. The case presented above illustrates further the striking effect of streptomycin on the *Proteus* organism. This effect has been demonstrated experimentally in the chick embryo,<sup>47</sup> and in disease of the genitourinary tract, good therapeutic results have been obtained.<sup>48</sup> Thus, a sharp reduction in the hitherto high mortality may be expected in the future.

### SUMMARY

Data on 52 cases of septicemia due to *Proteus vulgaris* reported in the literature are presented. These cases fell into two main groups: those associated with genitourinary-tract disease, and those associated with infection of the ear, nose and throat. Until the advent of streptomycin, the prognosis in these cases was poor.

A case cured by streptomycin is presented, and it is suggested that a striking reduction in mortality may be expected.

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## MEDICAL PROGRESS

### EPIDEMIOLOGY OF TULAREMIA IN MASSACHUSETTS WITH A REVIEW OF THE LITERATURE

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BOSTON

ALTHOUGH tularemia is considered a "truly American disease," Ohara<sup>1</sup> refers briefly to a historical account of a disease that he thinks was tularemia, described in 1837 by a Japanese physician, K. K. Homma.<sup>2</sup> Ohara states that Homma, under the heading of intoxication of rabbit meat, described in detail the incubation period and symptoms of a disease that, according to Homma, had not theretofore been described. After tularemia became known in America, physicians in the West claimed to have seen similar cases as early as 1907 in Arizona and 1909 in Missouri.

In 1911 McCoy<sup>3</sup> contributed the first information of the etiology of this disease by his discovery of what he called "plague-like disease of rodents" prevalent among the California ground squirrels,

first observed in squirrels received from Tulare County, California. McCoy and Chapin,<sup>4,5</sup> in 1912, discovered the causative organism of the disease in the California ground squirrels and named it *Bacterium tularense*,<sup>6</sup> after Tulare County. McCoy and Chapin,<sup>4,5</sup> in 1912, also reported complement fixation and agglutination of *Bact. tularense* by the serum of Chapin and a laboratory attendant, both of whom were extensively engaged in handling or dissecting infected rodents in the San Francisco laboratory and constituted the first cases of laboratory infection in man.

In Utah a disease of man was for several years popularly known as "deer-fly fever," owing to the belief that the infection was caused by the bite of the bloodsucking fly, *Chrysops discalis*, commonly found on horses. This belief found expression in a paper read before the Utah State Medical Association, Salt Lake City, on October 3, 1910, by

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‡Now more technically called *Paratuberculosis tularenis*.

Pearse,<sup>6</sup> of Brigham City, Utah. Pearse's cases constitute the first reported human cases of tularemia differentiated clinically, although the disease was not demonstrated to be tularemia until 1919.

Vail,<sup>7</sup> Sattler<sup>8</sup> and Lamb,<sup>9</sup> three ophthalmic surgeons of Cincinnati, Ohio, each reported a case of "conjunctivitis tularensis" in 1914, 1915 and 1917, respectively, in persons who had dressed rabbits and in whom the seat of primary localization was the conjunctival sac. The bacteriologic diagnosis of these 3 cases was made by Wherry and Lamb,<sup>10</sup> who isolated *Bact tularensis* on a culture medium from guinea pigs into which the eye scrapings had been injected. Vail's case is the first human case of tularemia on record to be diagnosed bacteriologically. Wherry and Lamb<sup>11, 12</sup> also isolated the organism from two wild cottontail rabbits found dead and collected in southern Indiana near the residence of Sattler's patient. This isolation from wild rabbits was the first bacteriologic proof of the rabbit reservoir of infection.

Francis,<sup>13, 14</sup> investigating "deer-fly fever" in Utah in 1919, recognized the identity of the Utah disease among human beings and the California ground-squirrel disease, and named the disease tularemia on account of the presence in the blood of the causative organism. He furnished proof of this identity by isolating *Bact tularensis* from 7 fly-bitten human patients, from 17 wild jack rabbits and from a ground squirrel, by demonstrating anti-tularensis agglutinins in his own blood and that of his assistant, both of whom had contracted the disease in the field laboratory, and by transmitting the infection among laboratory animals by the deer-fly, *Chrysops discalis*.<sup>15</sup>

Parker, Spencer and Francis,<sup>16</sup> of the United States Public Health Service, in the course of their studies of Rocky Mountain spotted fever at Hamilton, Montana, recognized the agency of the common wood tick of Montana, *Dermacentor andersoni*, as a host and transmitter of tularemia.

Dr J. Lawn Thompson,<sup>17</sup> of Washington, D. C., was the first to recognize a case of tularemia in the eastern United States when he made the diagnosis in a market man who was engaged in skinning and dressing wild rabbits in the Washington market in November and December, 1921. Francis<sup>18</sup> isolated virulent *Bact tularensis* from seven of 914 rabbit livers examined in the Washington, D. C., market in January, 1923.

Four articles in Japanese text, dealing with a disease of man occurring in Japan, were proved by Francis and Moore<sup>19</sup> to have been tularemia, although none of the articles contained specific mention of tularemia or of the published work of the American investigators on the disease. Two of these articles were by Ohara,<sup>1, 20</sup> one by Aoki, Kondo and Tazawa,<sup>21</sup> and one by Iwamoto, Muto and Aomura.<sup>22</sup> The dates of publication were between March 12, 1925, and July 10, 1925. Proof of the identity of

the American and Japanese diseases was furnished by Moore and Francis,<sup>19, 23</sup> who, on seeing Ohara's first descriptions, requested material from Ohara and demonstrated complete serologic and bacteriologic proof of the identity of the Japanese disease and tularemia of the United States.

Since the original discovery by McCoy in 1911, tularemia as an endemic disease of man has been observed in the forty-eight states, the District of Columbia and Alaska, it has been reported from Canada, Japan and the Soviet Union and, in recent years, in epidemic proportions from Europe (Sweden, Norway, Bohemia, Austria, Turkey and Germany).

### MODES OF TRANSMISSION

Tularemia is primarily a disease of certain rabbit-like mammals (Order *Lagomorpha*) and occasionally of certain rodents (Order *Rodentia*) and other wild mammals (shrew, opossum, beaver, coyote, red fox, gray fox and so forth) and game birds (sage hen, quail and grouse). A recently published list of vertebrates known to be naturally infected with tularemia includes, for the United States and Canada, six species of birds and twenty-eight species of mammals.<sup>24</sup> Although the disease is readily transmissible to man, human infections are only accidental. After recovery, one attack confers lifelong immunity.

### Contact

Human infections may be acquired from three main sources<sup>25</sup> the most common method, in eastern North America particularly, being by contact with a diseased animal. The bacteria may enter the human skin, which may be abraded or possibly even intact, or the mucous membrane (particularly that of the eyes) during the skinning and dressing of infected wild animals or while their skins are being handled. Thorough cooking kills the organism, however, infection may occur from eating raw or improperly cooked infected meat.<sup>26</sup> The disease has been known to be conveyed to people by the bite or the scratch of some infected animals. Self-inoculation by contact is prevalent among hunters, cooks and butchers, and there are often cases in large cities in which so-called "market fever" is well known among marketmen. Infection by contact is most frequent from November to January, during the hunting season, when cottontail rabbits, particularly, are for sale. Dogs and cats are susceptible, and have been known to contract the disease by eating raw meat of sick wild rabbits. In dogs, *Bact tularensis* may persist for many days without any outward symptoms.<sup>27</sup> Although the domestic rabbit is susceptible to experimental tularemia, rabbits raised in rabbitries have very rarely been found infected in this country and therefore may be handled and eaten with safety.<sup>28, 29</sup>

### Ticks

Tularemia is usually transmitted among wild mammals and birds by infected ticks, either by the bite or, more probably, by the feces that the ticks void while engorging on the host. Several species of ticks are known as natural or potential vectors. The rabbit tick, *Haemaphysalis leporis-palustris*, one of the most common ticks, has been found infected in nature<sup>10</sup> and transmits the disease in the laboratory.<sup>11</sup> Infected female ticks also pass on the bacterium to their eggs and larvae.<sup>12</sup> *H. leporis-palustris* is a particularly active transmitter, since all stages — larvae, nymphs and adults — occur often in unbelievable numbers on wild *Lagomorpha*, the adults being restricted to this type of host. Larvae and nymphs, however, often attach themselves also to migratory game birds, which may thus carry infected ticks over long distances and into new territory. It seems probable that *Bact. tularensis* survive the winter chiefly in infected *H. leporis-palustris*, which have been dropped off from infected cottontail rabbits dying of the disease.<sup>13</sup> All stages of this tick hibernate away from the host. The rabbit tick is not known to attack man and, therefore, is not instrumental in the transmission of tularemia from infected animals to human beings. The Rocky Mountain wood tick, *D. venustus* (Banks)\* is infected in nature in Montana.<sup>14,15</sup> It has also been proved that this tick is a true biologic host of *Bact. tularensis*, which it harbors not only in its feces but also in the epithelial cells of the digestive tract and malpighian tubes and in the celomic fluid. Furthermore, an infected female *D. venustus* will transmit *Bact. tularensis* to a certain percentage of its eggs, larvae and nymphs.<sup>11</sup> The presence of tularemia in the Pacific coast wood tick, *D. occidentalis* Currie, was demonstrated in California.<sup>16</sup> The eastern wood tick, *D. variabilis*, was found infected with the disease in nature, notably in Minnesota, by Green.<sup>17</sup> According to Philip and Jellison,<sup>18</sup> in this tick the bacteria may also be transmitted by an infected female to part of the progeny, through the eggs. However, in later investigations by Bell<sup>19</sup> no hereditary infection could be obtained, and it was concluded that such transmission appears to be of no significance for *D. variabilis*. Bell pointed out that the lack of difficulty of hereditary infection of the tick may be a most important limiting factor in the epizootic course of tularemia. He also demonstrated that infected *D. variabilis* feeding on immune or normal hosts lose their infection, presumably owing to the stimulating effect of the blood meal upon a normal bacteriocidal function of the ticks' gut. Before losing their infection as a result of feeding, such infected ticks may nevertheless inoculate a normal host, which will later on be a source of infection to other ticks feeding upon it. On the other hand, when fed upon an immune host, infected

ticks will not infect it, so that such an animal will not transmit the disease further to clean ticks. The number of animals that have become immune by a previous mild or chronic infection in a given area may also be of importance in limiting the spread of tularemia.

Wild rabbits and hares and their ticks are one of the most serious health problems, these animals being often infected with tularemia. Because many of them are handled by hunters, farmers, marketmen and consumers, they are a main source of human infection. All *Lagomorpha* are susceptible to the disease.<sup>20</sup> The snowshoe hare (*Lepus americanus*), the jack rabbit (races of *Lepus californicus*) and the cottontail rabbit (*Sylvilagus floridanus*) have all been found infected in nature. Among the *Lagomorpha*, tularemia is transmitted almost exclusively by *H. leporis-palustris*, rabbits and hares are the only efficient breeding host of this tick. The extent to which the larvae and nymphs of *D. variabilis* infect rabbits and hares in eastern North America is imperfectly known, however, some rodents, particularly the meadow mouse (*Microtus pennsylvanicus*), are the chief hosts of the larvae and nymphs of *D. variabilis*. The abundance of meadow mice is often closely correlated with the prevalence of *D. variabilis* in a given locality, such as the Cape Cod area and the neighboring islands. Little is known, as yet, concerning the natural occurrence of tick-borne diseases in the northeastern United States.

In the northeastern United States some human cases seem to have been caused by the adults of *D. variabilis*, which must have become infected in the immature stages, on wild life, but tick-borne infection of man is possible only when wood ticks are active, particularly from March to August.

### Other Bloodsucking Insects

The third method of transmission involves a variety of bloodsucking insects, such as the squirrel flea (*Ceratophyllus montanus*), the rabbit louse (*Haemodipsus ventricosus*), the squirrel louse (*Neohaematopinus laevisculus*), two western species of deer flies (*Chrysops discalis* and *C. nortyi*), some western species of horseflies (*Tabanus*), the stable fly (*Stomoxys calcitrans*), a species of the black fly (*Simulium kaimai*) and several species of mosquitoes (*Aedes aegypti*, *Aedes cinereus* and others). With all these insects, transmission has been effected under laboratory conditions from sick to healthy animals, either mechanically by the bite (interrupted feeding) or by the feces.<sup>21,22</sup> Such experiments do not, however, necessarily incriminate these insects as effective transmitters of the disease under natural conditions. In the northeastern United States, although several species of *Chrysops* are abundant and often attack people during the summer, they have been seldom incriminated in human cases of tularemia.

\*The same species as *D. andersoni* (Stiles).

### *Ingestion of Food and Water*

In recent years, a fourth possible source of infection has come to light—namely, drinking water contaminated by infected animals, particularly muskrats and beavers<sup>40-42</sup> Schuller and Erdman<sup>43</sup> describe an epidemic occurring in Germany during the summer of 1942, when 100 cases of tularemia were ascribed to the Dnieper River water and food in the township of Tchirin contaminated by mouse and rat excreta Khatenever,<sup>44</sup> in 1943, described an epidemic in Russia in which many patients were

occurring in central Russia that were due to threshing ricks contaminated by infected rodents Infection occurred by the inhalation of dust, giving rise to the typhoidal and pneumonic forms of the disease Similar epidemics are described by other Russian writers<sup>44, 47</sup>

### TULAREMIA IN MASSACHUSETTS

Prior to 1937 only 3 cases of tularemia in human beings were reported in Massachusetts, and it was definitely ascertained that these infections had their origin outside the Commonwealth However, in

TABLE 1 *Cases of Tularemia Reported in Massachusetts from 1929 to 1947*

CASE No	AGE yr	SEX	LOCALE	TIME	METHOD OF TRANSMISSION	INCUBATION PERIOD days	TYPE OF LESION	LABORATORY CONFIRMATION
1	48	M	Boston <sup>48</sup>	December, 1929	Skinning of rabbit from Illinois	3	Ulceroglandular (right index finger and arm)	Agglutination 1 640
2	—	M	Cumberland Island (off Florida) <sup>41</sup>	March, 1929	Wood tick or deer fly	?	Ulceroglandular	Agglutination 1 1280
3	32	M	Colorado	May, 1934	Handling or eating of wild rabbit	4	Glandular (? septicemic and pneumonic)	Agglutination 1 1280, Foshay skin test positive
4	10	F	Falmouth <sup>40</sup>	June, 1937	Dog (killing or eating wild rabbit, became ill 3 days after patient)		Typhoidol	Agglutination 1 1280, agglutination test on dog 1 40
5	6	F	Falmouth	June, 1938	Tick bite	1-5	Ulceroglandular (postauricular region)	—
6	48	F	Falmouth <sup>41</sup>	July, 1939	Tick bite	1-7	Ulceroglandular (posterior aspect of left thigh)	Agglutination 1 1280 Foshay skin test positive
7	38	M	Georgetown or Amesbury	November, 1941	Patient shot and skinned a wild rabbit	?	Ulceroglandular (right index finger and arm)	Agglutination 1 640
8	38	F	Falmouth	June, 1943	Tick bite	7	Pneumonic	Agglutination positive
9	38	M	Falmouth	August, 1943	? Tick bite, 6 weeks after case in wife (Case 8)	?	Pneumonic	Agglutination blood, 1 320 pleural fluid, 1 1280 P <i>tularenis</i> isolated from pleural fluid
10	52	M	Waltham	May, 1943	Insect bite (? tick)	3	Ulceroglandular (anterior aspect of thorax)	Agglutination 1 320
11	13	M	Scituate	November, 1944	Patient killed and skinned a wild rabbit	?	Ulceroglandular	—
12	11	M	Martha's Vineyard	August, 1946	Tick expelled from suppurating left supraclavicular abscess	?	Ulceroglandular (left eye and supraclavicular area)	Agglutination 1 1280
13	64	M	Boston	October, 1946	Contact (? vector) chef in restaurant	?	Pneumonic — ulceroglandular (left thumb)	Agglutination 1 1280
14	3	M	Bourne	June, 1947	Tick bite (on forehead)	?	Ulceroglandular	Agglutination 1 2560
15	58	F	Bourne	June, 1947	Tick bite	1	Ulceroglandular (left scapular region)	Agglutination 1 2560
16	68	M	Duxbury	June, 1947	Tick bite (on left leg)	?	Pneumonic	Agglutination 1 2560
17	—	F	Wareham	July, 1947	Tick bite (on scalp)	7-14	Pneumonic	Agglutination 1 1280

infected through eating and drinking material contaminated by infected field and house mice

Randerath<sup>45</sup> makes a reference to the origin of an outbreak among human beings during the winter of 1942-1943 on the eastern German front, where there had been an increase the previous autumn in field mice that had become infected from water rats When, at the onset of cold weather, the troops were housed, they came into contact with the mice, and cases of tularemia occurred He believed that food and water may have been the vehicles of transmission

### *Inhalation*

Another source of infection recently uncovered is inhalation Maisky,<sup>46</sup> in 1945, wrote of epidemics

1937 the first case of human tularemia definitely contracted in the Commonwealth was reported from Falmouth Since that time a total of 14 cases have been reported, 6 of these occurring in the last two years Furthermore, 8, or 57.2 per cent, of the cases have occurred on Cape Cod, 3 more, or 21.4 per cent in Plymouth County, which is adjacent to Cape Cod, and the remaining three, or 21.3 per cent, in the eastern part of the Commonwealth (Waltham, Georgetown or Amesbury and Boston) The ages varied from three to sixty-eight years, 6 female and 8 male patients being afflicted All patients recovered except 1 man (Table 1, Case 13), who died nine months after contracting the disease The type of disease varied, 7 patients having the ulceroglandular type 4 the pneumonic, 2 both ulceroglandular and

pneumonic, and 1 typhoidal. The diagnoses were confirmed by positive agglutination tests, which showed a maximum rise in titer, on the average, by the third week varying from 1:320 to 1:2560 in all but 2 of the cases. In 1 case (Table 1, Case 9), *Bact tularensis* was isolated from the pleural fluid after passage through guinea pigs and mice. The incubation period on the average was within seven days of exposure.

It is interesting to note that 8, or 57.2 per cent, of the patients were definitely ascertained to have been bitten by ticks, and 2 were probably bitten by ticks. Contact with rabbits was definitely established in 2 cases, contact with a dog that was infested with ticks and later manifested a positive agglutination for tularemia, with a titer of 1:40, was responsible for another case (Table 1, Case 4). In another case (Case 13) the source of infection could not be ascertained, except that it was probably by contact because the illness began with an infection of the thumb, pulmonic involvement eventually occurring. Furthermore, the patient worked as a chef in a restaurant, handling all sorts of meat but denying exposure to rabbits or rabbit meat.

Of the 8 patients infected by ticks, 5 lived on Cape Cod, 1 on Martha's Vineyard, and 2 in Plymouth County. Of the 2 probably infected by tick bites, 1 was located on Cape Cod and 1 in Waltham (metropolitan Boston). The case resulting from contact with an infested dog occurred on Cape Cod also. The 2 cases due to contact with rabbits occurred in Plymouth and Essex counties respectively.

### The Tick Problem

The south side of Cape Cod and the islands to the south—Martha's Vineyard, Nantucket and Naushon—are heavily infested. Ticks are less abundant on the north than on the south side of the Cape, and there are few to be found north of Plymouth, or inland beyond Middleboro and Taunton. Along the coast there is a marked diminution from Marion westward. *D. variabilis* (wood or dog tick), *H. leporis-palustris* (rabbit tick), and *Ixodes dentatus* are the most prevalent, however, *I. scapularis* (black-legged tick), *I. muris*, *I. marxi*, *I. cookei*, *I. brunneus* and *H. chordeilis* are also abundant.

The larvae and nymphs of *D. variabilis* engorge preferably on small rodents, which are the true breeding hosts of the immature instars. A few of these sometimes stray onto rabbits, larger mammals or birds, but it is questionable whether they are capable of moulting after engorging on these unusual hosts. The meadow mouse, *Microtus pennsylvanicus*, is the preferred host of larvae and nymphs in the Cape Cod area. Most adult forms attach to and engorge on large and medium-sized

mammals, the domestic dog being the favorite host. Man is readily attached to, but is only an accidental or stray host and not important to the survival of the species. In the Cape Cod area, adult ticks appear and are active from the latter part of April to the end of August.

The normal breeding hosts of adult and early stages of *H. leporis-palustris* are several species of hares and wild rabbits. Although this is the most important vector of tularemia in nature among rabbits and hares, it rarely bites human beings (as mentioned above), however, its larvae and nymphs are occasionally found on cats and dogs. Herman,<sup>22</sup> in 1938, found 18 out of 31 song sparrows infested with this tick on Cape Cod so that it can be distributed by the migration of birds.

*I. dentatus* appears to be a specific parasite of the *Lagomorpha* (rabbits and hares) at all stages,<sup>24</sup> but immature stages are sometimes found on rodents and birds. The normal hosts of the immature stages of *I. scapularis* are small mammals, particularly the white-footed mouse, but the adults attack a variety of large and medium-sized mammals straying occasionally onto man. *I. muris* appears to be at all stages a frequent parasite of small rodents, particularly the field mouse, occasionally, it attacks small migratory birds. *I. marxi* occurs normally on chipmunks and squirrels, and *I. cookei* infests medium-sized mammals, particularly *Garmipora*. *I. brunneus* and *H. chordeilis* are specific to birds. It is not yet known what part, if any, these ticks play in the transmission of tularemia.

It is readily conceivable how tularemia could be spread through the tick family and wild life once the infection has been introduced into a tick-infested area such as Cape Cod. *H. leporis-palustris* and *I. dentatus* could spread the disease from rabbit to rabbit, the former transmitting it to birds and the latter to field mice also. *I. brunneus* and *H. chordeilis* could spread it from bird to bird and *I. scapularis* and *I. muris* from mouse to mouse. In such a way a vicious circle could be formed, increasing the danger to man.

### The Rabbit Problem

Prior to 1937 no rabbits were imported privately from the West, however, 26,290 Western rabbits were liberated in Massachusetts in that year and up to and including 1940. Of these, 788 were released in the tick-infested counties of southeastern Massachusetts. The first case of tularemia appeared in Falmouth in June, 1937, whereas, the first shipment released in that area was in March, 1937. From then on, cases have appeared regularly in the area of high tick prevalence. It is interesting to note that all the cases occurring on Cape Cod have been on the south shore.

In March, 1941, a shipment of cottontail rabbits was released in the vicinity of Lawrence, Massachusetts, and in November of that year a case of

tularemia was reported from that area, resulting from the skinning of wild rabbits shot in hunting

In 1940, at the request of the Division of Fisheries and Game of the Massachusetts Department of Conservation, Belding and Merrill<sup>55</sup> examined post mortem 136 rabbits that had been imported by Massachusetts game clubs and had died in transit or shortly after their arrival in Massachusetts. Two of these rabbits were found to have tularemia. A previous series, in 1937, revealed no infection in 194 imported rabbits; therefore, the prevalence of tularemia in 2 out of 330 rabbits (0.6 per cent) was taken to correspond closely with the usually accepted incidence of 1 per cent infection among wild rabbits. The 2 tularemic rabbits were found in the shipments coming from Missouri and Arkansas (states with a total of 583 and 322 human cases reported for the period extending from 1937-1940).

The imported rabbits were admitted to Massachusetts under certification by accredited health authorities at the shipping points. The certificates stated that there had been no epidemic of tularemia or rabbit fever in the last two years in the counties in which the rabbits were trapped, and that these counties were free from contagious and infectious rabbit diseases. The presence of tularemia in certified rabbits from two states indicates that such guarantees are inadequate to prevent the inclusion of tularemic rabbits in these shipments.

Although there were no importations from 1942 to 1945, 4 cases of tularemia were reported during this period (2 from Cape Cod, 1 from Plymouth County, and 1 from Waltham). Three of these cases were ascribed to ticks, and 1 to contact with wild rabbits.

During 1946 approximately 3000 wild rabbits were again imported, mostly from Arkansas and Kansas, into Massachusetts by game clubs. Although none were released on Cape Cod, some were released in Bristol and Plymouth counties. During 1946 a case of tularemia was reported from Martha's Vineyard, and another from Boston. However, in 1947 there were 2 cases in Bourne (Cape Cod), and 2 in Plymouth County.

#### DISCUSSION

From the material presented above, it appears that tularemia did not exist in Massachusetts prior to 1937. Although the medical profession had known about the disease since 1911, no cases except the 3 contracted outside the Commonwealth were reported prior to that year. In the spring of 1937 the first importations of wild rabbits from the midwestern states began, and the first case of tularemia definitely contracted in Massachusetts was reported during the following summer from the tick-infested area of the Commonwealth.

The fact that these wild rabbits were imported from areas where tularemia was prevalent and that some were proved to be infected with tularemia, in

spite of certification from the exporting areas, leads one to believe that the disease was introduced into Massachusetts by this means.

Although these wild rabbits were released throughout the Commonwealth, only the tick-infested regions of Cape Cod and Plymouth County have persistently reported sporadic cases of tularemia because of the prevalence of ticks to maintain the focus. Fortunately, although ticks can spread and maintain a focus, there have been no outbreaks of any consequence in Massachusetts. This may be due to certain factors, as yet not fully known, limiting the spread of infection, even though the reservoirs and vectors are present in variable numbers. However, since there has been a regular occurrence of cases of tularemia in the tick-infested areas from 1937, one can assume that there is a small endemic focus in Massachusetts. The future of this focus cannot be predicted so far as its maintenance is concerned, however, its spread can be prevented by control of the tick population and by the placing of definite restrictions upon the introduction of fresh animal hosts and possible reservoirs such as wild rabbits.

The control of the tick population can be approached in several ways, none of which are very satisfactory in the ultimate eradication. Destruction with insecticides such as nicotine sulfate, sodium fluoride and DDT solutions is of value only on a very limited scale. Destruction of wild animal hosts as a means of eliminating the ticks from a given area seems an impossible task, for the arachnids are numerous and varied among both mammals and birds. The use of insect parasites such as the chalcid flies, if they became well established, could conceivably do much to reduce the tick population by killing a percentage of the nymphs. However, the two known chalcid parasites of ticks (*H. hookeri* and *I. caucurteri*) do not seem to be particularly attracted by *D. variabilis*, hence, their introduction is hardly an effective control measure for this tick.

Individual protective measures against ticks by man can be the most important factor in the avoidance of tularemic infections. Walking in woods and pastures should be avoided as much as possible during the tick season, if such walks are unavoidable, adequate clothing covering as much of the body as possible should be worn. Upon return from a heavily infested area, clothing should be removed and treated with some insecticide, and the body searched for any attached ticks. Particular care should be taken not to crush the ticks when removing them, since the infection can be acquired in this way. Ticks should also be removed from all household pets such as dogs before they are allowed to enter the house.

It has been shown that certification by authorities of exporting areas is inadequate in the prevention of the exportation of infected animals. Neither is the inspection of shipments at the point of release satis-

factory, for the disease is too easily overlooked in the gross Guinea-pig inoculations have been demonstrated to be the only sure method of diagnosis and identification, but this is expensive and impractical because it is applicable only to dead rabbits. Inasmuch as tularemia exists in practically all states exporting rabbits, the best safeguard against the introduction and spread of tularemia in Massachusetts seems to be the banning of the importation of cottontail rabbits from the West.

## SUMMARY

The history of tularemia is discussed, beginning with a description of a disease with a similar symptom complex by Homma in 1837 and including the monumental work by various men of the United States Public Health Service, who established the disease as a definite entity with specific causal relations.

The following modes of transmission are presented whereby man is infected by contact with infected wild animals, by ticks, by bloodsucking insects, by ingestion of contaminated food and water, and by inhalation.

The reported incidence of tularemia in Massachusetts consists of 14 cases occurring in ten years, with 78.7 per cent occurring in the southeastern sector (Cape Cod and Plymouth County area), 57.2 per cent were due to tick bites, 14.3 per cent were probably due to tick bites, 14.3 per cent were due to contact with infected rabbits, 7.1 per cent were due to contact with an infected dog and 7.1 per cent were due to contact with unknown sources.

Ticks capable of transmitting tularemia, particularly *Dermacentor variabilis*, *Haemaphysalis leporispalustris* and *Ixodes dentatus*, are most prevalent on the south side of Cape Cod and islands to the south, with diminishing numbers in Plymouth County and northward.

The appearance of tularemia in Massachusetts coincides with the beginning of importations of wild rabbits from midwestern states where tularemia is prevalent, and their release in the tick infested area of the Commonwealth. The existence of tularemia in these imported rabbits was proved in 1940 and a 1 per cent incidence was calculated.

Satisfactory means of controlling the tick population have not yet been devised. Personal prophylaxis against ticks is very important in the avoidance of infection.

Certification of imported wild rabbits is inadequate in the prevention of the introduction of tularemia into a previously tick-free state.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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### CASE 34061

#### PRESENTATION OF CASE

A twenty-six-year-old married woman entered the hospital complaining of abdominal pain.

Two days before admission she began having generalized, crampy abdominal pain. She had a small bowel movement that day. On the following day she was unrelieved following a good bowel movement. She experienced some anorexia, but no nausea or vomiting. On the day of admission, the pain moved to the right lower quadrant and became steady. Examination of the blood by a physician showed a white-cell count of 12,000 and hospitalization was advised.

The patient was believed to be pregnant, her last period having occurred just two months previously. Her appetite had been "picky" for a month.

Examination showed tenderness and only slight spasm at McBurney's point, with cough and rebound tenderness. Rectal examination disclosed a tender

right vault, high up, and a normal left vault. The cervix was tender to motion. The uterus was enlarged and consistent with a two months' pregnancy.

The temperature was 98.6°F, the pulse 82, and the respirations 20. The blood pressure was 125 systolic, 70 diastolic.

Urinalysis was negative.

Immediately following admission, preoperative medication was given and operation performed.

#### DIFFERENTIAL DIAGNOSIS

DR GORDON SCANNELL. I assume that the enlarged uterus, in addition to the missed period, was the reason for thinking that this patient was pregnant—I should like to know if she had had children, because if she had been pregnant before and thought that she was pregnant, she was probably right. If she had not had children I should like to know how long she had been married.

DR MARSHALL K BARTLETT. This was her second pregnancy. She was seen by an obstetrician on the day of admission. He thought that she had a normal two months' pregnancy.

DR SCANNELL. In summary, this was a young married woman with a short history representing an acute surgical condition of the abdomen. We will therefore, on the date given, rule out chronic diseases and focus our attention on the immediate problem as it faced the surgeon on the night of admission. The symptoms were referable to the lower part of the abdomen and pelvis, there were definite signs of peritoneal irritation—namely, slight spasm at McBurney's point, and cough and rebound tenderness. Then too we have the signs of tenderness in the cul-de-sac and on motion of the cervix, which cannot be dismissed. If we are considering the pelvis and the acute problem, we think

of three systems the urinary tract, the gastrointestinal tract and the genital tract. I believe that we can rule out the urinary tract. This was not a good history for pyelitis, although we think of that in a person with an early pregnancy. The patient had no fever, the urine was normal, and there was no characteristic radiation of pain and no other data on which to justify that diagnosis.

When we come to the gastrointestinal tract we come to the obvious problem, which I am sure played a large role in the mind of the surgeon taking care of the patient. The thing to rule out — by operation, if necessary — is appendicitis. She did have a short history, with a shift of the pain from generalized abdominal to the right lower quadrant that is one of the cardinal symptoms of appendicitis. She had anorexia, which often occurs instead of nausea and vomiting, thus, one frequently sees acute appendicitis with the patient complaining of not having desire for food that day. On the other hand, nausea and vomiting are expected in an acute appendiceal disease, especially when one is thinking of the acute obstructive type, which is so dangerous. This patient had an elevated white-cell count and localized signs at McBurney's point. Against appendicitis, in addition to the absence of nausea and vomiting, is the absence of bowel symptoms. She had a normal bowel movement on the day before admission and a small one on the previous day that may have been normal. She did not give the history of mild constipation that so regularly goes with an acute appendicitis. The bowels move a little, but there is no satisfactory bowel movement. So much for appendicitis at the moment. Since we do not have to make the final decision, we can assume the academic point of view and say that she did not have enough to go with acute appendicitis. If appendicitis was present, it does not impress one as the acute obstructive type.

One might think of a Meckel's diverticulum, but I rule it out on the basis of the absence of obstructive symptoms and the presence of right-sided localization of the pain.

Gastroenteritis is a common catch-all diagnosis. This patient had neither gastric nor enteric symptoms.

Carcinoma even in this age group is important. We occasionally see carcinoma of the cecum or carcinoma of the appendix that may give this picture and lead to an operation for an acute condition. However, we have no data on which to base that diagnosis. There are other things that we might think of, such as diverticulitis of the cecum and a twisted epiploic appendix, both of which result in prominent bowel symptoms, of which this patient had no complaint.

Turning from the gastrointestinal tract to the pelvic organs, I think that we may find more fertile ground. I would rule out pelvic inflammatory

disease. She had no fever, was apparently not very sick and had no profuse menstrual irregularity of flow. She did not have the physical findings to go with it. A twisted cyst of some kind should be considered. The history is compatible with that diagnosis. She had vague, generalized abdominal pain shifting to one side and going low in the abdomen, with a slight suggestion of bowel symptoms but not very much. I assume that if she had a twisted cyst large enough to make her thus sick, the cyst would have been palpable. Furthermore, with a twisted cyst I would expect nausea and vomiting. In fact we have expected these symptoms right along but have not observed them.

The one diagnosis that we arrive at is the question of an ectopic pregnancy. Against that diagnosis there is only one real factor and not a really good argument against it. The patient had no bleeding, which is common in ectopic pregnancy. But there is no reason for bleeding irregularly at this point, unless there is rupture of the pregnancy, or leakage. In favor of extrauterine pregnancy are a good many things: the menstrual history and the skipped period, and something happening on one of the expected days of a period, which is not uncommon with ectopic pregnancy. She had the subjective symptoms of pregnancy, tenderness referred to the pelvis, and particularly tenderness on motion of the cervix. A pelvic appendix can also give tenderness on motion of the cervix but the factor *par excellence* that gives such tenderness is a little bleeding behind the uterus in the cul-de-sac or bleeding in one tube with tenderness high up on the right. Because it is high, there could well have been a small swelling in the right tube, which was tender, but could not be nicely delineated as an ovarian tumor.

The whole picture seems to be that of pelvic irritation. The very vague abdominal complaints without subsequent involvement of the gastrointestinal tract point to the uterus or ovaries. As the best possibility I would select ectopic pregnancy, which had just started to abort, causing leakage of blood into the cul-de-sac. The patient had not had a ruptured ectopic pregnancy in the dramatic sense.

A PHYSICIAN. I should like to say that I have seen a very similar picture in a patient who had a fibroma of the uterus that had degenerated.

DR. SCANNELL. I think that is a real possibility, especially with associated pregnancy, although I think that it might be picked up as an irregularity of the uterus on examination.

DR. BARTLETT. I saw this woman shortly after she was admitted and thought that she probably had acute appendicitis. The signs were rather well localized although we realized that they were not very striking. The tenderness was not of great magnitude and the spasm was minimal. We had

the benefit of feeling the uterus, which was large for an ectopic pregnancy and more like that of a normal pregnancy. I was somewhat comforted by the fact that the obstetrician, who was an experienced man, thought that it was a normal intra-uterine pregnancy. In any case we could not rule out appendicitis. We operated on her with that preoperative diagnosis.

#### CLINICAL DIAGNOSIS

Acute appendicitis

DR SCANNELL'S DIAGNOSIS

Ectopic pregnancy

#### ANATOMICAL DIAGNOSIS

*Twisted cyst of serosa of cecum*

#### PATHOLOGICAL DISCUSSION

DR BARTLETT When the peritoneum was opened there was a small amount of blood-tinged fluid in the peritoneal cavity. The appendix was normal. The terminal ileum was normal. There were abnormal lymph nodes in the mesentery. We could find no Meckel's diverticulum, and both tubes and ovaries were entirely normal. A low hanging cecum extended down over the pelvic brim and was delivered into the wound. Hanging from the posterior wall behind the base of the appendix was a pedunculated cyst the size of an English walnut. The stalk was about 3 cm long. The cyst was thin walled and had a 360° twist in its pedicle. The omentum was adherent to the surface of the cyst. Even then we did not know what it was. It was well on in the evening, but Dr Castleman was in the hospital and he came over and looked at it. The thing that occurred to me was the possibility of some queer second implantation of another ovum, but it did not seem to be that, and Dr Castleman agreed. The cyst was removed very easily, and the patient made an uneventful recovery.

DR BENJAMIN CASTLEMAN In gross the specimen looked like a paraovarian cyst that had twisted and at the site of the twist was a small hematoma, which resulted from the twist. The wall was thin and contained straw-colored fluid with a bit of hemorrhage in it as a result of the twist. On microscopic examination no definite diagnosis could be made except that of cyst. It probably was congenital in origin. It is conceivable that it might have been an appendix epiploica that had slowly twisted, with resultant central necrosis and cystification. The few twisted appendices epiploicae that I have seen have all been on the left side in the sigmoid, where there are more fat tabs. These, then, are the two possibilities: a congenital rest or a twisted appendix epiploica that had degenerated.

DR BARTLETT I have never seen anything like this. I would be interested to know if anyone has

seen a cyst of this type arising from the cecum or anywhere in the gastrointestinal tract.

DR FALLS B. HERSHEY Do not ovarian cysts occasionally move from their attachment to the ovary?

DR CASTLEMAN It would not have been implanted on the posterior wall of the cecum.

DR HERSHEY Does a reduplication from that area ever give this picture?

DR CASTLEMAN I have never seen one as small as this. It was 2 or 3 cm in diameter.

DR RICHARD H. SWEET I have seen cysts arising from embryonic rests in connection with the ovary. I recall a case in this hospital, in which operation was performed by Dr George A. Leland. It was a sizable cyst, however, ovarian in origin.

DR CASTLEMAN There is no evidence for that here.

### CASE 34062

#### PRESENTATION OF CASE

A sixteen-year-old high-school boy entered the hospital complaining of fever, sweats, aches and pains.

He had been in excellent health all his life until three months before admission, when he first noticed a dull aching pain in the legs and pelvic bones. The pain was mild at first, being present only on walking, and after a week was replaced by a vaguely localized but persistent aching of the right leg, mainly in the muscles rather than in the joints, that was worse at night and not particularly aggravated by motion. The pain was often severe enough to prevent sleeping and, in spite of heat treatments, grew gradually worse. X-ray studies of the spine at that time were negative. The patient was not acutely ill until three weeks before entry, when he was awakened by a severe aching pain across the lower back and was found trembling and perspiring profusely. The following morning the temperature was 100°F. Within two or three days the backache subsided, but he began to notice pleuritic pain in the left anterior portion of the chest and later on the right side as well. He was given sulfonamide tablets for a week but continued to have an irregular fever, the temperature ranging up to 102°F, profuse sweating and generalized muscle aches as well as pleuritic pain. An x-ray film of the chest taken one and a half weeks after the onset of these symptoms was said to show "virus pneumonia." After two weeks the temperature came down somewhat. The patient was then given penicillin in wax on two consecutive days. After each injection the temperature rose higher, and he felt worse. On the day before entry the temperature reached 103°F. There had been no coryza, cough or gastrointestinal symptoms except for anorexia.

Physical examination showed a well nourished boy, who was rather well developed for his age. He seemed inattentive, restless and irritable, but not in distress. The gums were slightly reddened and tender, and the throat was moderately injected. Considerable tenderness was elicited just anterior to the sternomastoid muscles on both sides of the neck. This tenderness seemed to be over several pea-sized, deep lymph nodes. No other adenopathy was noted. The heart was of normal size, with a generalized soft, blowing systolic murmur. The abdomen was normal, the liver and spleen were not palpable.

The temperature was 101.6°F, the pulse 110, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

Urinalysis showed a specific gravity of 1.010, a + test for albumin and a 0 test for sugar. The hemoglobin was 10.5 gm, and the white-cell count 3200. The differential count revealed 89 per cent small lymphocytes and 11 per cent "atypical lymphocytes" and no polymorphonuclear leukocytes. The platelets were normal. Widal, Brucella, tularemia and heterophil-antibody agglutinations were negative. An x-ray film of the chest was clear.

In the hospital the patient continued to run a low-grade fever, his condition growing slowly but progressively worse. After two and a half weeks the blood smear showed numerous large cells that were thought to be monoblasts or stem cells. The white-cell count, after an initial drop to 1400, rose steadily to as high as 40,500 after a few weeks. Differential counts continued to show a virtual absence of polymorphonuclears and numerous atypical monocytes and "blast" forms each averaging about 40 per cent of the total. Additional x-ray films of the chest revealed small areas of increased density scattered throughout the lower lobes. This process on repeated x-ray examination seemed to become more marked, and the areas of density somewhat confluent. X-ray studies of the cervical spine and ribs disclosed no definite evidence of bone destruction. During the fourth hospital week x-ray examination of the skull showed a soft-tissue mass in the right frontal area just anterior to the coronal suture. There appeared to be destruction of the outer table underlying it. The patient was given several blood transfusions but failed steadily, and expired approximately five and a half weeks after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. BERNARD M. JACOBSON This case is obviously one of acute leukemia. The initial symptoms in this patient are extremely common in most cases of acute leukemia—namely, those suggestive of infection and bone and joint disease. During the three months before the patient entered the hospital the differential diagnosis could have been extended to a large number of different conditions, including virus infection, rheumatic fever, brucellosis, ery-

thema nodosum, periarteritis nodosa and lupus erythematosus. During the three weeks before entry the patient undoubtedly had pleural or pulmonary infection with regression, as noted by the first normal chest film after entry. We are not told anything regarding the blood picture during these three months, but it is easily imaginable that the blood morphology was nondiagnostic.

After entry the first physical signs that can be related to the later established diagnosis are redness and tenderness of the gums and cervical lymphadenopathy. The soft, blowing systolic murmur does not indicate organic heart disease but is more likely to be due either to the fever or to the anemia. The clinical course included fever and the development of increased areas of infiltrates in both lungs. The last chest film that I viewed appeared to show dilatation of the heart, diffuse pulmonary infiltration and pleural effusion, more marked on the right side. The presence of only minimal lymphadenopathy and the absence of splenomegaly are quite common in acute leukemia.

The initial blood examination revealed an anemia and a leukopenia. Although we are not informed of the course of the hemoglobin this level must have fallen significantly during the remainder of the hospital stay. In most of the smears the red cells were generally slightly macrocytic, with only slight variation in size and shape, and were well filled with hemoglobin. The platelets appeared normal or slightly reduced. The appearance of the red cells is certainly compatible with a myelophthisic anemia.

The most striking laboratory finding is the white-cell picture. I had the opportunity to study six blood smears. The initial smear revealed a majority of the white cells to consist of apparently mature small lymphocytes, but within four days the picture had changed. The remaining smears showed successively large numbers of cells, which varied in size from that of a normal monocyte to two or three times as large as a normal monocyte. Many of the cells showed serrated margins suggestive of pseudopodia. The cytoplasm ranged from lightly basophilic to intensely basophilic, often vacuolated and with or without a moderate number of azurophilic granules. The nuclei of these cells were either round or oval or reniform or even lobulated, with a skin-like coarse chromatin and containing one or more nucleoli. The most mature of these cells appeared to be intermediate between the mature monocytes and the obvious blast forms and can be termed promonocytes. The blast forms with extremely large and serrated margins looked unlike myeloblasts or lymphoblasts and can be called monoblasts. The changes in the white-cell picture during the course of the disease are not uncommon in monocytic leukemia and have recently been well described.\*

\*Rappaport, A. E. and Kurel, V. H. Monocytic leukemia. *Blood* 2:333-355, 1947.

Three clinical features of this disease can be readily explained by the diagnosis of monocytic leukemia. The initial bone and joint symptoms were possibly due to leukemic infiltrations of the periosteum or juxta-articular bone of the lumbar spine, pelvis and femurs. The later pulmonary findings are more likely to have been due to leukemic infiltrates rather than to infection. Finally, the soft-tissue mass noted in the right frontal area of the skull was probably also due to a leukemic tumor. Whether this tumor had the appearance of a chloroma or not I cannot predict.

During the early part of the hospital stay the abnormalities of the white cells could have reasonably brought up the question of leukemoid monocytic reaction in various diseases such as tuberculosis, lymphoma, lupus erythematosus and subacute bacterial endocarditis, as well as the monocytic phase sometimes seen in agranulocytosis. The later appearance of numerous blast forms, however, rendered these possibilities extremely unlikely.

In view of the complete absence of myeloblasts and myelocytes in the blood smears I believe that we can dismiss the possibility of the Naegeli type of monocytic leukemia — that is, a variant of myelogenous leukemia.

My diagnosis is acute monocytic leukemia.

DR LOWREY F DAVENPORT: It might be well to emphasize the earlier weeks of this patient's illness before abnormal cells appeared in the blood stream. We were confronted with a fever of unknown origin, enlarged cervical lymph nodes and a complete absence of granulocytes. For a time we hoped that the condition was an agranulocytosis following sulfadiazine, which had been given elsewhere. The enlarged cervical lymph nodes and a progressive increase in the mononuclear cells temporarily raised the hope of infectious mononucleosis. In fact we built a very strong circumstantial case on this premise. This boy's roommate had had, two weeks prior to the patient's initial symptoms, an episode of fever with enlarged lymph nodes that could have been infectious mononucleosis. Unfortunately, no blood studies were made. For several weeks, then, we proceeded on the assumption that this more hopeful diagnosis was possible. It was not until the appearance of large numbers of abnormal cells in the peripheral blood that the possibility of an infectious mononucleosis masked by agranulocytosis was dismissed.

#### CLINICAL DIAGNOSIS

Acute monocytic leukemia

#### DR JACOBSON'S DIAGNOSIS

Acute monocytic leukemia.

#### ANATOMICAL DIAGNOSES

*Lymphatic leukemia*

*Leukemic infiltration of bone marrow, spleen, lymph nodes, liver, kidneys, lungs, testicles, pericardium, pleura and voluntary muscle*

Hydrothorax, bilateral, slight

Ulcers, nonspecific, of esophagus, stomach and small intestine

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY: This case, as Dr Davenport pointed out, was very confusing until the blood picture in the last few weeks of life became frankly leukemic. A large proportion of the cells were extremely immature, but the hospital hematologists who saw the smears agreed with Dr Jacobson that the cells were probably monoblasts. I could reach no other conclusion myself when I reviewed the blood smears. The autopsy findings, however, were inconsistent with a diagnosis of monocytic leukemia, and I am at a loss to explain the discrepancy.

Widespread leukemic infiltration was present in the bone marrow, lymph nodes, spleen, thymus, liver, kidneys, testicles and lungs, as well as many tumor-like masses in skeletal muscles and serosal tissues. None of these tumors had the greenish color of chloromas. The pulmonary infiltration was particularly extensive. It was almost exclusively interstitial but so extensive that the intervening alveoli were completely collapsed and the tissue seemed solidly consolidated.

The problem of the case lies in the nature of the cells composing the infiltrate. They were similar in all areas and appeared in the fixed tissue sections to be characteristic, quite mature lymphocytes. The cells were small, the cytoplasm scanty and basophilic, and the nuclei predominantly round with peripheral chromatin and few conspicuous nucleoli. No cells of the large, very immature type, so numerous in the peripheral blood, were to be found, and very few cells that suggested monocytes in any stage of development were present. I am forced on the basis of the anatomic material to make a diagnosis of lymphatic leukemia, and you will have to choose for yourselves whether to trust the clinical or the anatomic evidence.

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## STREPTOMYCIN FOR URINARY-TRACT INFECTIONS

THERE are now several recognized methods that have been employed with varying success in the treatment of urinary-tract infections. Methenamine with acid phosphate is somewhat effective as a urinary antiseptic. Acidification of the urine with mandelic acid or one of its salts has proved useful in many cases. The sulfonamides, however, have proved much more successful in the simple acute infections. Since gram-positive organisms that are susceptible to penicillin are infrequent as causes of infection of the urinary tract, that antibiotic has only limited uses in this field. On the other hand, streptomycin should prove more useful in the therapy of these infections since it is the most

effective agent now available against the gram-negative bacilli that are the predominant bacterial agents in infections of the urinary tract.

The results of streptomycin treatment of urinary-tract infections have not proved universally favorable. In 409 cases collected by the Committee on Chemotherapeutics and Other Agents of the National Research Council,<sup>1</sup> the over-all recovery rate was only 42 per cent. Similar results were obtained in many clinics. Perhaps the most important causes of such failures reside in the nature of the infections that are treated. That is particularly true of chronic cases of pyelonephritis in which there are underlying anatomic defects that interfere with proper drainage, as well as destructive processes that are difficult to heal and remain the source of persistent infection or sites for reinfection. It is just these conditions that also interfere with the success of other forms of therapy that have usually been used without benefit in these cases before streptomycin was tried.

One of the most important causes of streptomycin failures, however, is the rapid replacement of streptomycin-sensitive organisms in the urine by organisms that are highly resistant to streptomycin. In many cases the resistant bacteria have increased more than eight-thousandfold in a matter of a few hours after the first dose of streptomycin was given.<sup>2</sup>

Since the development of resistant bacteria in vitro is usually accomplished by exposing organisms to subeffective concentrations of the antibacterial agent, it is supposed that the use of massive doses of streptomycin would prevent the development of resistant bacteria in the urine. Unfortunately, the range of streptomycin dosage that is feasible in human beings is very narrow, and the upper limit of such doses is not much greater than the amounts that are therapeutically effective. The use of maximum doses, therefore, has not proved successful in preventing the appearance of resistant strains that interfere with the efficacy of therapy.<sup>3</sup>

Alkalinization of the urine, however, has proved extremely useful in this respect. It has been shown that within the range of reaction attainable in the urine—namely, between pH 5.5 and 8.0—the antibacterial effect of any given concentrations of streptomycin may be increased up to eightyfold.<sup>4</sup> A

Three clinical features of this disease can be readily explained by the diagnosis of monocytic leukemia. The initial bone and joint symptoms were possibly due to leukemic infiltrations of the periosteum or juxta-articular bone of the lumbar spine, pelvis and femurs. The later pulmonary findings are more likely to have been due to leukemic infiltrates rather than to infection. Finally, the soft-tissue mass noted in the right frontal area of the skull was probably also due to a leukemic tumor. Whether this tumor had the appearance of a chloroma or not I cannot predict.

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Acute monocytic leukemia

#### DR JACOBSON'S DIAGNOSIS

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The Dispensary Food Clinic, at the time of its establishment, was a unique experiment of its kind and has been the model for over fifty similar clinics that have been set up throughout the world. Here patients have learned the bearing of diet on their individual health problems, with consideration given to their religious and racial backgrounds and their economic situations.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**MANSFIELD**—James A. Mansfield M.D., of Boston died on June 29. He was in his eighty-first year.

Dr. Mansfield received his degree from Jefferson Medical College of Philadelphia in 1896.  
A son survives.

**POLIAK**—Mendel Poliak M.D. of Springfield died on September 15. He was in his sixty-first year.

Dr. Poliak received his degree from Université de Montpellier Faculté de Médecine in 1922. He was a member of the staff of Wesson Memorial Hospital.

**RICKER**—Carroll H. Ricker M.D. of Worcester, died on September 6. He was in his eightieth year.

Dr. Ricker received his degree from Tufts College Medical School in 1907. He was a member of the staff of Worcester City Hospital and was a fellow of the American Medical Association.

His widow and a daughter survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### TRICHINOSIS IN MASSACHUSETTS

The problem of trichinosis is much larger than is generally realized. In the ten-year period 1936-1945, a total of 287 cases were reported to the Massachusetts Department of Public Health with 7 deaths. Cases have been reported with regularity from all areas, a total of eighty-one different communities reporting one or more cases during the ten-year period. However, there can be little doubt that many times as many persons were so mildly ill of trichinosis as never to have come under medical care.

Surveys of autopsy material in various localities throughout the United States have shown an incidence of trichinosis infections varying from 16 to 36 per cent. It is generally recognized that man becomes infected by eating trichinosis pork, which in turn comes from hogs fed on garbage containing scraps of uncooked trichinosis pork. The average incidence of trichinosis among hogs in the United States during the past fifty years has remained practically unchanged at a level of approximately 1.5 per cent. It has been estimated that 96,849,000 hogs were slaughtered in the United States during 1944, and the total production of pork was 12,893,000,000 pounds.

This amount of pork would furnish about 30,000,000 individual servings, or approximately 200 servings per person in the United States, of which 3 would contain trichinae. Since the average length of life of Americans is now over sixty-four years and an average of 200 servings of pork are annually eaten per person, for the lifetime of each person nearly 200 meals of pork containing trichinae are consumed.

Another way of visualizing the magnitude of the problem in Massachusetts is to estimate the number of persons acquiring the parasites. Each year about 70,000 persons are added to the population by births. Even at the lowest estimate 16 per cent of this number, or 11,200, should show symptoms each year instead of the average of less than 30 cases actually reported annually during the last ten years.

The onset of the illness is of variable intensity, depending upon the amount of infected meat eaten and the abundance of trichinae in the meat. The first symptoms are generally gastrointestinal, consisting of nausea, vomiting, abdominal pain and diarrhea lasting for three to five days. These are followed by a period of muscular aching, pain and tenderness, chills, a temperature not unlike that in typhoid fever, cough, edema of the eyelids and skin rash. Not infrequently, signs and symptoms of pulmonary, cardiac and central-nervous system involvement are found. This period of peripheral symptomatology lasts as long as the adult worm is producing larvae—five to seven weeks. Death occurs most frequently from the third to the sixth week. Although recovery is usually complete, vague rheumatic pains may persist for about a year.

The most frequent laboratory aid is the elevated eosinophil count. The precipitin test is highly sensitive but is negative early in the illness, three to four weeks often being required before it is elevated. The skin test is of value if there is first an initial negative response followed by a positive reaction at a later date. Muscle biopsy, if positive, makes the diagnosis certain.

Various measures have been advocated in the control of trichinosis, including destruction of rats, elimination of garbage and offal from the feed of hogs, cooking of garbage to be fed to hogs, proper processing of pork products customarily eaten without cooking, microscopical inspection of pork and education of the public in the necessity of adequately cooking pork and pork products.

Processing of pork and its products means the treatment by freezing, cooking, smoking, curing or other methods that will render nonviable any trichinae present in the meat. Cooking and freezing are the easiest and most readily accessible methods. Trichinae are killed at a temperature of 55°C (131°F). Federal regulations require that, in the killing of trichinae by heat, all parts of the meat be raised to a temperature of 58.3°C. (137°F), the American Public Health Association recommends



that all fresh pork and its products be cooked at a temperature and for a time sufficient to allow all parts of the meat to reach a temperature of at least 65°C (150°F)

Trichinous meat in sections of 15 cm or less can be rendered noninfectious by refrigeration at a temperature of 5°F (−15°C) for twenty days, −10°F (−23°C) for ten days or −20°F (−30°C) for six days. It has also been found that raw pork in commercial quantities may be rendered free of infective trichinae by reduction of its temperature to −35°C (−31°F) for a short time or by freezing at −17.8°C (0°F) for seventy-two hours. In ground meat, encysted trichinae are killed in a few minutes at a temperature of −17.8°C (0°F). In most deep-freezing cabinets, such as those used in the home, temperatures varying from 0 to 5°F are usually maintained, and thus another method of assuring trichina-free meat has become available to the individual consumer.

Recently the President's committee for the conservation of food recommended that meat should not be overcooked. However, it is important that the consumer should not go to the other extreme of undercooking meat, particularly pork and its products, unless he is unreservedly certain that it has been properly processed beforehand.

#### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1947

##### RÉSUMÉ

DISEASE	DECEMBER 1947	DECEMBER 1946	SEVEN-YEAR MEDIAN
Chancroid	6	0	2*
Chicken pox	1680	1337	1444
Diphtheria	37	87	21
Dog bite	620	556	517
Dysentery bacillary	19	4	12
German measles	64	67	68
Gonorrhea	262	316	316
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	2	0	0*
Malaria	7	7	7
Measles	459	840	840
Meningitis, meningococcal	1	9	12
Meningitis, Pfeiffer-bacillus	8	8	3
Meningitis, pneumococcal	3	7	7†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	0	0	1†
Meningitis, undetermined	5	2	2†
Mumps	1267	318	670
Pneumonia, lobar	96	114	232
Poliomyelitis	7	17	11
Salmonellosis	9	10	5
Scarlet fever	475	664	978
Syphilis	274	238	376
Tuberculosis, pulmonary	226	207	207
Tuberculosis, other forms	14	13	13
Typhoid fever	4	3	4
Undulant fever	4	2	3
Whooping cough	682	730	730

\*Three-year median

†Five-year median

##### COMMENT

Diseases above the seven-year median are chicken pox, diphtheria, dog bite, bacillary dysentery, mumps and salmonellosis.

Diseases below the seven-year median are lobar pneumonia, measles, meningococcal meningitis, poliomyelitis and scarlet fever.

Chicken pox showed a marked increase in December, bringing the year's total to the second highest since 1916. Mumps reached the highest peak of the year in December,

which probably indicates that 1948 will be a mumps year. The seasonal increase in diphtheria continues, returning to the level of the late spring of 1947.

Only one case of meningococcal meningitis was reported after seven years of high prevalence in which 60 cases were once reported in December.

Scarlet fever dropped to the second lowest level ever reported, the total for 1947 being the lowest since 1905. Although the incidence of measles is low, the usual seasonal increase has brought the total to three times the number of cases reported for November.

##### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anthrax was reported from Franklin, 1, total, 1.  
 Diphtheria was reported from Bedford, 1, Boston, 9, Brookline, 5, Chelsea, 2, Chicopee, 1, Everett, 1, Holyoke, 2, Malden, 2, Revere, 8, Somerville, 6, total, 37.  
 Dysentery, bacillary, was reported from Clinton, 1, Greenfield, 1, Salem, 1, Swampscott, 3, Worcester, 13, total, 19.  
 Malaria was reported from Boston, 1, Lawrence, 1, Marion, 1, Medford, 2, Northampton, 1, Uxbridge, 1, total, 7.  
 Meningitis, meningococcal, was reported from Worcester, 1, total, 1.  
 Meningitis, Pfeiffer-bacillus, was reported from East Longmeadow, 1, Everett, 1, Lawrence, 2, Quincy, 2, West Springfield, 1, Worcester, 1, total, 8.  
 Meningitis, pneumococcal, was reported from Cambridge, 1, Holliston, 1, Pittsfield, 1, total, 3.  
 Meningitis, undetermined, was reported from Boston, 1, Pittsfield, 1, Somerville, 1, Springfield, 1, Worcester, 1, total, 5.  
 Poliomyelitis was reported from Cambridge, 1, Framingham, 1, Northampton, 1, Rockland, 1, Sherborn, 1, Southboro, 1, Worcester, 1, total, 7.  
 Salmonellosis was reported from Belmont, 1, Cambridge, 4, Montague, 1, New Bedford, 1, Revere, 1, Swampscott, 1, total, 9.  
 Septic sore throat was reported from Boston, 1, Merrimack, 3, Milton, 1, total, 5.  
 Trachoma was reported from Worcester, 1, total, 1.  
 Trichinosis was reported from Cambridge, 2, Pittsfield, 1, Salem, 1, Stoneham, 1, total, 5.  
 Typhoid fever was reported from Boston, 1, Fall River, 2, Newton, 1, total, 4.  
 Undulant fever was reported from Attleboro, 1, Boston, 1, Danvers, 1, Rutland, 1, total, 4.

#### MISCELLANY

##### SCHOLARSHIPS FOR NURSES

The Greater Boston Nursing Council recently announced that scholarships and loan funds for students are available at the nurses' training schools of the following institutions: Beth Israel Hospital, Mt. Auburn Hospital, Children's Hospital, Faulkner Hospital, Massachusetts General Hospital, Massachusetts Memorial Hospitals, New England Deaconess Hospital, Newton-Wellesley Hospital, Peter Bent Brigham Hospital, Simmons College, Boston College, Melrose Hospital, and New England Hospital for Women and Children.

##### NOTE

The following appointments to the teaching staff of Harvard Medical School were recently announced: Frederick Chapman Robbins, of Bronxville, New York (A.B. University of Missouri 1936, M.D. Harvard University 1940), assistant in pediatrics; Henry Mitchell Putnam of Westwood (Ph.B. Yale University, M.D. Harvard University 1935), assistant in pediatrics; Walter Higbee Caskey, of Cambridge (M.D. Harvard University 1946), research fellow in comparative pathology and tropical medicine; Victor Clarence Vaughn, III, of Richmond, Virginia (A.B. Harvard University 1939, M.D. Harvard University 1943), research fellow in pediatrics; Samuel Waldfogel, of Detroit, Michigan (S.B. Wayne University 1938, M.A. University of Michigan 1939, Ph.D. University of Michigan 1946), research associate in psychiatry; Ronald Charles Sniffen, of Milton (M.D. University of Toronto 1936), instructor in pathology; Edgar Breck Taft, of Cambridge (M.D. Yale University School of Medicine 1942), instructor in pathology; Dante Francesco Campagna-

Pinto of Cambridge (A B Harvard University 1939, M D Harvard University 1943) assistant in pathology John Merrill Craig of Berkeley, California (A B University of California, 1936 M A University of California 1938 M D Harvard University 1941) assistant in pathology Melvyn Bertram Black, of Boston (A B Harvard University 1940 M D Harvard University 1943) research fellow in pathology Gilcin Finley Meadors, Jr of Washington D C (S R Mississippi College 1936 M D Tulane University of Louisiana 1940 M P H Johns Hopkins School of Public Health and Hygiene 1947) instructor in preventive medicine John Platt Hubbell Jr of Brooklyn (A B Williams College 1940 M D Harvard University 1943) assistant in pediatrics Donald Emerson McLean of Winchester (A B Harvard University 1938 M D Harvard University 1943) assistant in pediatrics Harold Edelhoch of Bronx New York (A B New York University 1943 A M Princeton University 1946, Ph D Princeton University 1947) research fellow in physical chemistry Drummond Ellis of Glasgow Scotland (B Sc Glasgow University 1944) research fellow in physical chemistry James Alexander Wolff of Boston (A B Harvard University 1935, M D New York University College of Medicine 1940), research fellow in pediatrics Arthur Francis Battista of Ontario Canada (B Sc McGill University 1943 M D C M McGill University 1944 M Sc University of Western Ontario 1947) research fellow in physiology Harold Scarborough of West Yorkshire, England (M B Ch B University of Edinburgh Scotland 1932 Ph D University of Edinburgh Scotland 1938) research fellow in physiology Melvin Hyman Kaplow, of Cambridge (A B Harvard University 1942) Harold C Ernst, fellow in bacteriology and immunology, Doreen Nightingale, of Loodoo England (M R C S, L R C P University College Hospital Medical School 1939 M B B S Looch University College Hospital Medical School 1940, M S Lond and F R C S England 1945), research fellow in surgery John Butler Tomkins of Waverley (S B Wesleyan University 1926 M D Tufts College Medical School 1935) instructor in psychiatry and Jacques Lewin of Paris France (M D Faculté de Médecine Paris 1929 Licence en Sciences Faculté des Sciences Paris 1933 M D (Diplôme d'Etat) Faculté de Médecine Paris 1947) research fellow in physical chemistry

### NATIONAL INSTITUTE OF HEALTH

Establishment of an experimental-biology and medicine institute, in the National Institute of Health of the United States Public Health Service has been announced. The new research institute will combine the functions of the Division of Physiology and the Pathology and Chemistry Laboratories and will permit greater co-ordination of scientific investigations.

Dr William Henry Schrell Jr, chief of the Division of Physiology, has been named director of the new institute and he will also serve as associate director of the National Institute of Health.

Formation of the Institute is part of a wider organization of the National Institute of Health, according to Dr Thomas Parran, surgeon general of the Public Health Service. Four other divisions and laboratories engaged in scientific research will also be consolidated into two additional institutes all of which will be modeled after the National Cancer Institute.

### BAY STATE SOCIETY FOR CRIPPLED AND HANDICAPPED

The Bay State Society for the Crippled and Handicapped has made a grant of \$12,000 for the work of the Sezure Unit of the Neurological Institute at the Children's Medical Center in Boston.

### HOSPITAL SURVEY AND CONSTRUCTION ACT

As of January 9, according to the Washington Report on the Medical Sciences 92 applications for construction of hospitals, dispensaries and health centers under the Hill-Burton Hospital Survey and Construction Act has been approved. The estimated outlay will be \$40,765,702 of which the Federal Government will provide \$13,381,548. The states so far included in the list are Alabama, Florida, Illinois, Indiana, Kentucky, Mississippi, New Mexico, North Carolina, Oklahoma and Texas.

## CORRESPONDENCE

### SHORTAGE OF NURSES

To the Editor: I read with interest the editorial "Shortage of Nurses," which appeared in the January 1 issue of the *Journal*.

You may know that House Bill 90 which has been filed with the 1948 General Court of Massachusetts, if enacted, would permit registration by women at the age of twenty rather than twenty-one a point discussed in the editorial.

In the light of information obtained by our Personnel Policies and Practices Committee we question the statement that the average nurse in Massachusetts works only a forty-four hour week. There is a trend in that direction but statistics show forty-eight hours to be the average work week in this area.

We thank you for the editorial and the points made in it especially your plea to exert every effort to obtain for nurses their proper recognition and economic stability.

HELENE G LEE, Executive Secretary  
Massachusetts State Nurses Association

420 Boylston Street  
Boston

### FURTHER NOTES ON FOLIC ACID

To the Editor: It has been a great help to me to have been able to follow, through the many articles published in the 1947 issues of the *Journal* the conflicting studies on the use of folic acid in the deficiency syndromes associated with macrocytosis of the red cells. I am referring to particular to the two progress reports "Hematology," by Dr William Dameshek to the September 18 and 25 issues and the more recent ones on "Pteroylglutamic Acid and Related Substances," by Dr Frederick Sargent, II, in the October 30 and November 6 issues.

The consensus seems to be that folic acid and related substances help in the control of the two manifestations of deficiency syndromes associated with macrocytosis of the red cells—namely changes in the gastrointestinal tract and changes to the blood and blood forming organs—but that folic acid has no influence on the third manifestation—changes in the central nervous system which is the most serious with the resulting subacute combined degeneration of the spinal cord.

Words of warning on the use of folic acid even for the control of the first two manifestations of the deficiency syndrome have been sounded. I refer in particular to the opinion of Dr Russell L Hadeo of the Cleveland Clinic who wrote, in an article entitled "Treatment of Pernicious Anemia" (*Postgraduate Medicine* 1:131-135, 1947) that he was relying on liver extract for the present, because folic acid in his opinion had as yet an undetermined place in treatment. More recently, in the Boston issue (September 1947, number) of the *Medical Clinics of North America* Drs Helen V Belding and Joseph F Ross in an article entitled "Recent Advances in Hematology," have stressed the very definite therapeutic limitations of folic acid in the deficiency syndrome associated with macrocytosis. The fact that folic acid is an effective hematopoietic agent in the anemia characterized by macrocytosis and a megaloblastic bone marrow is not denied but the authors stress what is the most important point in my opinion, that folic acid not only has little influence in altering the changes in the central nervous system but also is unable to prevent them from developing even though the hematologic status remains normal. More recently another warning of disastrous consequences has been given against the use of folic acid even in the control of the changes in the gastrointestinal tract and in the blood and blood forming organs, in spite of the many articles in the recent literature regarding its efficacy in the control of these two manifestations of the deficiency syndrome associated with macrocytosis. Dr O C Hansen Pruss in an article entitled "Relapse of Patients with Pernicious Anemia Receiving Folic Acid" (*American Journal of the Medical Sciences* 214:465-468, 1947) reports 2 patients who were suffering from pernicious anemia and relapsed while receiving folic acid; these patients responded well to liver extract.

It seems to me as a practicing physician that in answer to the patient with the deficiency syndrome associated with macrocytosis who demands the use of the new drug

appeared on the medical horizon, I should reply after analyzing the data submitted to you that by using folic acid he would in the light of present knowledge be taking considerable risk and be spending considerable money, whereas by taking liver extract he would be obtaining sure and proved control and at the same time be saving considerable money

GABRIEL F GRECO, M D

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Ozone Park 16, New York

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Methods of Vitamin Assay* Prepared and edited by The Association of Vitamin Chemists, Incorporated. 8°, cloth, 189 pp. New York: Interscience Publishers, Incorporated, 1947. \$3.50.

This standard manual was compiled by a committee of scientists recognized as authorities in vitamin research, with the assistance of a large staff of competent reviewers who were not members of the Association. The scope of the book is limited, since only such methods are included as have been successfully used by several committee members, thus representing the combined knowledge and experience of many persons. Special chapters are devoted to each of the important vitamins, and each chapter concludes with a selected list of references to the vitamin under discussion. The manual is recommended as a reference source for all medical and laboratory libraries.

*The American Illustrated Medical Dictionary* A complete dictionary of the terms used in medicine, surgery, dentistry, pharmacy, chemistry, nursing, veterinary science, biology, medical biography, etc., with their pronunciation, derivation, and definition. By W. A. Newman Dorland, A. M., M. D. Twenty-first edition. 8°, cloth, 1660 pp., with 880 illustrations. With the collaboration of E. C. L. Miller, M. D. Philadelphia: W. B. Saunders Company, 1947. \$8.50.

This standard, authoritative dictionary, last published in 1944, has been revised to include the voluminous medical terminology resulting from the research of the war years. In addition to the actual war medicine and surgery, new words have been added in the fields of tropical medicine, aviation medicine, medical zoology and mycology, biochemistry and pharmacology, including antibiotics, enzymes, vitamins and endocrines, and physics and nucleonics, including the application of radioactive isotopes. The names of proprietary medicines have been reviewed, and obsolete terms have been eliminated from the present edition. The book is well published in every way and should be in all medical and public libraries and institutions and also is recommended to all physicians and persons needing an up-to-date medical dictionary.

## NOTICES

### ANNOUNCEMENTS

Dr. Thomas J. Anglen and Dr. Knowles B. Lawrence announce the association with them of Dr. Martin L. Bradford in the practice of general surgery at 1180 Beacon Street, Brookline.

Dr. Bernard Bloom announces the opening of his office for the practice of urology at 67 Chestnut Street, Springfield.

Dr. Kurt H. Thoma announces the association of Dr. Daniel J. Holland, Jr., in the practice of oral surgery, and the removal of their offices to 1180 Beacon Street, Brookline.

Dr. Robert S. Thomson announces the removal of his office for the practice of general surgery to 866 Main Street, Fitchburg.

## MASSACHUSETTS MEDICO-LEGAL SOCIETY

The winter meeting of the Massachusetts Medico-Legal Society will be held in the George Burgess Magrath Library, Department of Legal Medicine, Harvard Medical School, on Wednesday, February 11, at 2:30 p.m.

### PROGRAM

Business Meeting

Beryllium Pneumoconiosis Walter W. Jetter, M.D.

Blood Concentrations of Barbiturates in Relation to Toxic Effects R. S. Fisher, M.D., and J. T. Walker, Ph.D.

Multiple Foci of Acute Myocardial Necrosis Resulting from Systemic Anoxia Richard Ford, M.D.

Collation

## FELLOWSHIPS IN PUBLIC HEALTH

Fellowships leading to a master's degree in public health in the field of health education are again being offered to any qualified United States citizen between the ages of twenty-two and forty.

Candidates must hold a bachelor's degree from a recognized college or university at the time the application is filed, and must be able to meet the entrance requirements of the accredited school of public health of their choice. Proof of acceptance at such a school must be furnished before applications are submitted to the Fellowship Awards Committee for consideration. In addition to the bachelor's degree, courses in the biologic sciences, sociology and education are required. Training in public speaking, journalism and psychology and work in public health or a related field are considered desirable.

The fellowship consists of eight or nine months of academic work, which begins with the fall term in 1948, and three months of supervised field experience in community health-education activities in a local health department. The academic training includes courses in public-health administration, epidemiology, public-health and school education, problems in health education, community organization, information techniques and others.

Information and application blanks may be obtained from the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

## AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

The annual meeting of the American Association of Pathologists and Bacteriologists will be held at the Jefferson Medical College, Philadelphia, on Friday and Saturday, March 12 and 13. Half a day will be devoted to a consideration of "Diseases of Bones." Contributions to this symposium are invited, but all material should reach the Secretary not later than Saturday, February 14. All papers, including illustrative material, must be presented within a limit of ten minutes.

Further information may be obtained from the Secretary, American Association of Pathologists and Bacteriologists, 2085 Adelbert Road, Cleveland 6, Ohio.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 12

#### FRIDAY, FEBRUARY 13

\*9:00-10:00 a.m. Recent Advances in Our Knowledge of Blood Coagulation. Dr. Benjamin Alexander. Joseph H. Pratt Diagnostic Hospital.

\*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

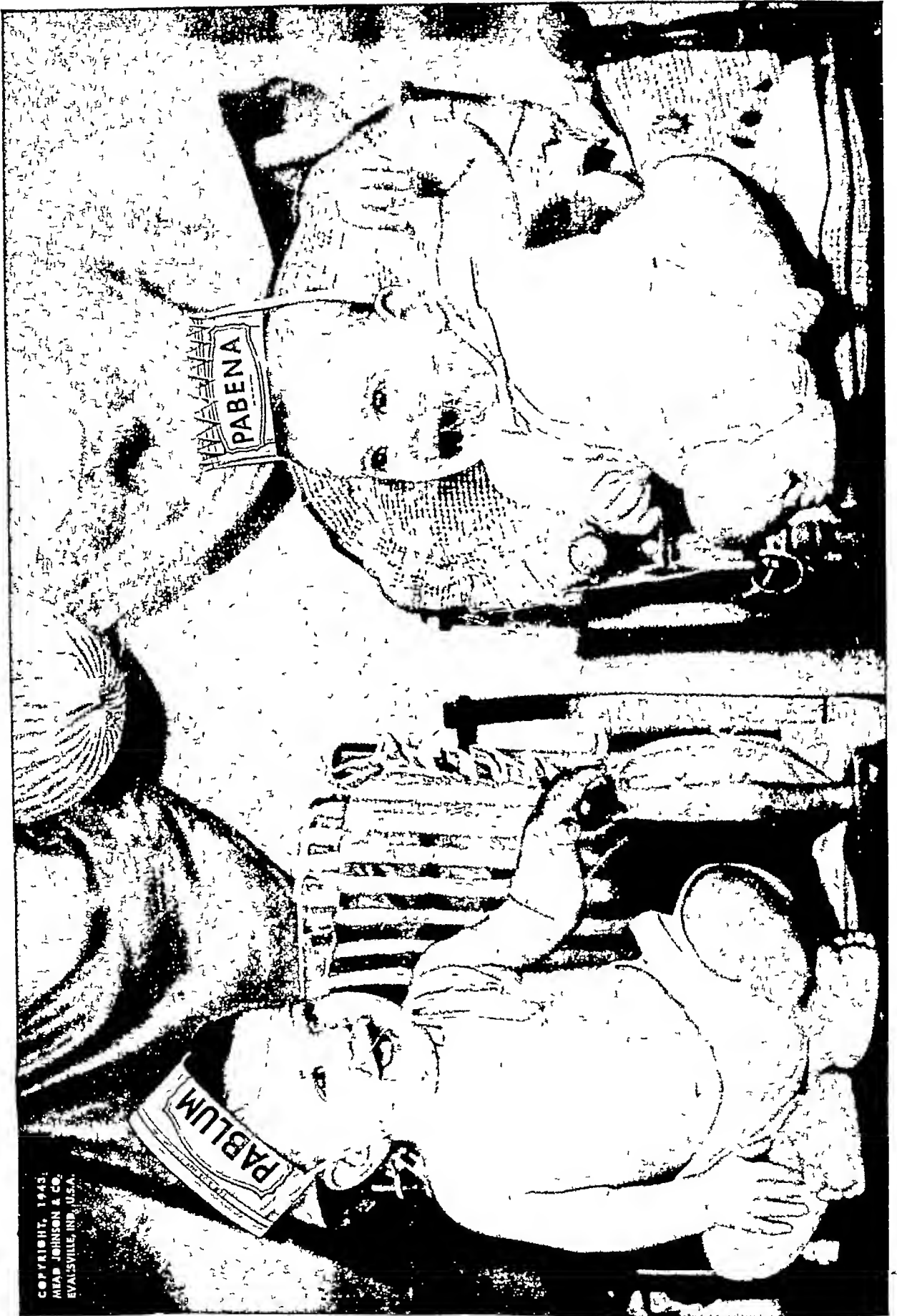
12:00 p.m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

#### MONDAY, FEBRUARY 16

\*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

(Notices concluded on page 2111)





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## PNEUMONIA AT THE PHILADELPHIA GENERAL HOSPITAL, 1936-1946\*

HAROLD L. ISRAEL, M.D.,† ROBERT C. MITTERLING, M.D.,‡ AND HARRISON F. FLIPPIN, M.D.§

### PHILADELPHIA

IN RECENT years pneumonia has rapidly become less important as a cause of death. There has been a sharp decline in admission of patients with pneumonia to most hospitals and recent studies on the effectiveness of modern therapy of pneumonia have indicated a low case mortality. Nevertheless, at the Philadelphia General Hospital, pneumonia remains a serious problem, and the impression has been obtained that in late years the response of patients with pneumonia to specific therapy has not been so dramatic as that observed in earlier years. The present study was projected to verify this impression, and to determine if possible the responsible factors.

### MATERIAL

The records of adult patients discharged from the Philadelphia General Hospital with the diagnosis of primary pneumonia in three representative years were studied. The year from July 1, 1936, to June 30, 1937, was one in which specific therapy was not available, the year from July 1, 1940, to June 30, 1941, saw the widespread use of sulfonamides and in the year from July 1, 1945, to June 30, 1946, penicillin was available as an adjuvant to or substitute for the sulfonamides.

In an effort to exclude secondary pneumonias, consideration was restricted to patients less than sixty years of age. Cases of tuberculous pneumonia and postoperative and terminal pneumonia were also excluded. In all other patients, the final recorded clinical or pathological diagnosis was employed.

Patients treated in the special pneumonia wards of the hospital, except when admitted *in extremis*, had routine laboratory studies comprising sputum culture, blood culture and complete blood counts. These data are not complete in many cases treated in other wards. Typing of pneumococci was done

routinely in 1936-37 and 1940-41 but, in 1945-46, only 60 pneumococci isolated from blood or exudates. The later years of the study saw increased use of x-ray examination on admission. Other data included the duration of illness and the type of medical care prior to admission, the maximum fever and the incidence of complications. The case mortality rates were calculated both for all admissions and for admissions of patients surviving twenty-four hours. The number of febrile days in the hospital, as well as the total hospital stay of recovered patients, was determined as a further indication of the therapeutic response.

### FREQUENCY OF PNEUMONIAS ACCORDING TO DIAGNOSIS

The total number of cases studied was 368 in 1936-37, 540 in 1940-41 and 420 in 1945-46 (Table 1). In each year approximately 95 per cent or more of the cases were classified as lobar pneumonia or bronchopneumonia. Other bacterial pneumonias, caused by *Klebsiella pneumoniae*, streptococci, staphylococci, *Haemophilus influenzae* and *Salmonella* comprised 4.0 per cent of the total in 1936-37, 1.3 per cent in 1940-41 and 1.4 per cent in 1945-46. The diagnosis of viral pneumonia was made in single cases in 1936-37 and 1940-41, but in the 1945-46 season, similar diagnoses, in this report grouped as viral pneumonias, were made in 14 cases, or 3.4 per cent of the total for the year.

Analysis of the clinical and laboratory characteristics of the two major groups, lobar pneumonia and primary bronchopneumonia, revealed lesser differences than are commonly considered to exist between these two types (Table 2). It appears that the distinction was made in most cases on the basis of the x-ray or pathological report, for the other characteristics did not seem to vary sufficiently to permit a sharp differentiation of the groups. The differences were rather constant, however, in each of the years: patients diagnosed as having bronchopneumonia had a somewhat higher mean age, a slightly longer mean duration of symptoms, slightly less fever and a less marked leukocytosis on admission, sputum culture slightly less often demon-

\*From the Medical Service, Philadelphia General Hospital.

†This study was aided by a grant from The Research Fund for Infectious Diseases, University of Pennsylvania.

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Associate professor of medicine, Graduate School of Medicine, University of Pennsylvania; visiting physician, Philadelphia General Hospital.

strated pneumococci, and positive blood cultures were less frequent in the bronchopneumonias. The frequency of higher types of pneumococci was greater also in this group. The case mortality tended to be higher in the bronchopneumonias, and among the recovered patients in this group the duration of fever and hospitalization tended to be less. It appears that the differences between primary lobar pneumonia and bronchopneumonia in each of the years under study were slight and that the two groups showed parallel changes from one year to the other. These observations indicate the difficulty of clinical differentiation and support the modern tendency to classify the pneumonias on an etiologic basis.

Although on this basis it seems justifiable to combine the two groups for purposes of further analysis, this has not been done since the criteria for diag-

that reported in studies made in the early years of sulfonamide therapy.<sup>2,3</sup> Also notable in the 1940-41 season were the slightly increased mean age of the patients, the reduction in white-cell count and the short duration of fever after admission — the temperature was normal within forty-eight hours of admission in 57.6 per cent of patients receiving specific drug therapy.

There were 312 patients with lobar pneumonia in 1945-46. In 10 cases specific therapy was not received. Sulfadiazine alone was employed in 119 patients, a sulfadiazine-sulfamerazine combination in 34 patients, penicillin alone in 36 patients and penicillin in addition to sulfonamides in 113 patients. Nevertheless, the case mortality failed to show a further decline but rose slightly. The mean age of the patients rose sharply, and leukocytosis was significantly less marked. There was a dis-

TABLE 1 Primary Pneumonias by Diagnosis among Patients under the Age of Sixty

DIAGNOSIS	JULY 1, 1936-JUNE 30, 1937		JULY 1, 1940-JUNE 30, 1941		JULY 1, 1945-JUNE 30, 1946	
	NO OF PATIENTS	NO OF DEATHS	NO OF PATIENTS	NO OF DEATHS	NO OF PATIENTS	NO OF DEATHS
Lobar pneumonia	261	80	429	43	312	38
Bronchopneumonia	91	31	103	15	87	12
Pneumonia due to Friedländer bacillus	2	2	6	5	1	1
Streptococcal pneumonia	7	2	—	—	1	0
Staphylococcal pneumonia	3	0	1	1	2	0
Influenzal pneumonia	3	2	—	—	2	1
Salmonella pneumonia	—	—	—	—	1	1
Viroid pneumonia	1	0	1	0	14	0
Totals	368	117	540	64	420	53

nosis of primary bronchopneumonia are poorly defined and are not uniformly applied in all localities. Lobar pneumonia, on the other hand, is commonly considered to be a well defined entity, generally and uniformly recognized. For this reason, the remainder of this investigation is confined to patients with the diagnosis of lobar pneumonia.

The 261 patients with lobar pneumonia in 1936-37 received merely supportive treatment with the exception of 5 cases in which serum therapy was employed. In all respects the clinical and laboratory characteristics of the whole group are typical of those reported in the extensive American studies made before the introduction of serum therapy.<sup>1</sup> The mean age of thirty-five years and nine months, the mean white-cell count of 20,300 on admission and the case mortality of 23.3 per cent are noteworthy because of the changes in these characteristics noted in ensuing years.

In 1940-41 there were 429 patients with lobar pneumonia, 20 of whom failed to receive sulfonamides because of erroneous diagnoses on admission. Sulfadiazine was used in 184, sulfathiazole in 174 and sulfapyridine in 51 patients. Five patients received serum in addition. The sharp decline in the case mortality — to 5.4 per cent — is typical of

tinct increase in mean duration of fever and of hospitalization, the incidence of patients who were afebrile in forty-eight hours was only 39.0 per cent. This was true regardless of the type of therapy used in the hospital. The case mortality varied in a remarkable fashion according to the therapy employed: patients receiving sulfonamides alone had a rate of 1.4 per cent, whereas those receiving penicillin had a rate of 12.0 per cent. This is not inconsistent with the excellent results obtained with penicillin in controlled studies and is merely an indication that all patients recognized as seriously ill received penicillin.

The rise in case mortality of lobar pneumonia observed in 1945-46 is not statistically significant when treated by the chi-square method, but it is remarkable in view of the additional availability of penicillin. There is ample evidence for the effectiveness of penicillin in lobar pneumonia, and the rise in mortality cannot be attributed to the use of penicillin instead of sulfonamides. Actually, the apparent slight increase in mortality was probably not due to chance but rather, as demonstrated below, to alterations in the age distribution of the patients. However, the patients with lobar pneumonia in 1945-46 showed a highly significant difference, the probability that the result was due to chance





being less than 0.0001, from those of 1940-41 in two respects: the decrease in white-cell count and the increased duration of fever after application of specific therapy. A possible explanation for these changes is that an increased prevalence of non-bacterial pneumonias during the war years had resulted in the erroneous inclusion of a considerable number of viroid pneumonias in the group with diagnoses of lobar pneumonia. Another possibility is that a change in the character of pneumococcal lobar pneumonia had occurred.

#### INFLUENCE OF AGE

As pointed out above, the mean age of patients with lobar pneumonia increased from 1936-37 to 1945-46 (Table 2). Table 3 emphasizes this change

remained essentially constant by age groups from 1940-41 to 1945-46. In the latter year, in all age groups except the few patients from ten to nineteen years old, the white-cell count was decidedly lower, and the therapeutic response as measured by critical decline of temperature was considerably less satisfactory (Table 3).

The duration of illness, type of medical care, degree of fever and x-ray findings did not vary consistently with age. The frequency of positive blood cultures was greater in the older age groups.

#### INFLUENCE OF SEX AND RACE

Case mortality rates in 1936-37 showed no remarkable difference between males and females or whites and Negroes (Table 4). Similar observations

TABLE 5 *Relation of Admission White-Cell Count to Response in Patients with Lobar Pneumonia*

YEAR	WHITE CELL COUNT	NO OF PATIENTS	CASE MORTALITY		PATIENTS AFEBRILE IN FORTY- EIGHT HOURS†
			TOTAL %	CORRECTED* %	
July 1, 1936, to June 30, 1937	$\times 10^3$				%
	under 5.0	4	50.0	50.0	—
	5-9	24	16.7	4.8	—
	10-14	42	31.0	29.3	—
	15-19	50	12.0	12.0	—
	20-29	62	12.9	10.0	—
	over 29	36	41.7	34.4	—
July 1, 1940, to June 30, 1941 (treated cases)					
	under 5.0	5	20.0	0	75.0
	5-9	55	9.1	5.7	61.2
	10-14	76	7.9	2.8	57.2
	15-19	112	4.5	4.5	55.2
	20-29	108	4.8	4.8	56.6
	over 29	31	3.3	3.3	58.6
July 1, 1945, to June 30, 1946 (treated cases)					
	under 5.0	9	44.5	16.7	40.0
	5-9	73	9.6	4.3	40.6
	10-14	70	5.7	4.4	37.5
	15-19	55	14.5	13.0	38.3
	20-29	45	6.7	4.5	29.3
	over 29	9	11.1	11.1	25.0

\*Corrected by exclusion of patients dying within twenty-four hours of admission.

†Among patients who recovered.

and indicates that the apparent increase in mortality in the last year was due to the changing age distribution of the patients with lobar pneumonia. It will be noted that in 1936-37 the group of patients from thirty to thirty-nine years of age was the largest, with almost equal numbers in the younger and older groups, in 1940-41 there was a slight increase in the older age groups, but in 1945-46 there was a marked increase, the groups of patients between forty and forty-nine and fifty and fifty-nine each being larger than any of the younger groups.

Analysis by age groups demonstrates the same sharp increase in seriousness of lobar pneumonia with age that was noted in older reports before the introduction of chemotherapy.<sup>1</sup> The use of sulfonamides resulted in a sharp reduction of mortality in all age groups, the case mortality above the age of fifty, however, remained high. Although the rate re-

have been the rule in the past.<sup>1</sup> In the patients receiving specific therapy in 1940-41 and 1945-46, the reduction in case mortality appeared equally striking among white females and Negroes of both sexes, whereas the rate among white males showed a considerably less satisfactory decline. The significantly higher average age of the white males in 1945-46 may have accounted for the high mortality in that year, but the average age of this group in 1940-41 was not markedly higher than that of the other groups. The greater frequency of alcoholism among white males may have been important, although it did not cause a greater mortality in 1936-37.

In both sexes and both races, the decrease in white-cell count and prolongation of fever mentioned above were noted in the 1945-46 group, even though the case mortality was little higher

than in 1940-41. No consistent sexual or racial differences were noted in duration of illness before hospitalization, character of prior medical care, degree of fever or bacteriologic or x-ray studies.

#### SIGNIFICANCE OF WHITE-CELL COUNT

Analysis indicates that the initial white-cell count was not correlated with response to therapy (Table 5). Patients with counts below 5000 showed an extremely high mortality, but the number of such cases was small. With this exception there seemed no constant tendency in any year for the response to therapy to vary with the white-cell count.

In 1936-37 only 12.8 per cent of patients had counts below 10,000, and 45.0 per cent had counts of 20,000 and above; in 1940-41, 15.3 per cent had counts below 10,000 and 36.0 per cent counts of 20,000 and more, whereas in 1945-46 the corre-

a more rapid decline of fever than the patients with moderate or with marked leukocytosis.

The degree of leukocytosis showed no consistent relation with age, sex, race or bacteriologic or x-ray findings.

#### BACTERIOLOGIC EXAMINATION

Sputum cultures were obtained in 67.4 per cent of the lobar pneumonias in 1936-37, in 78.6 per cent in 1940-41 and in 71.6 per cent in 1946-47. In the first of these years, pneumococci were demonstrated either in pure culture or with other organisms in 90.9 per cent, in 1940-41, in 93.2 per cent, and in 1945-46, in 92.4 per cent. The pneumococci isolated from sputum showed considerable variation in 1936-37, Type I, 16.0 per cent, Type II, 10.6 per cent, Type III, 8.9 per cent, Type IV, 1.2 per cent, Type VIII, 1.8 per cent and Type X and higher,

TABLE 6. *Influence of Therapy before Admission*

PREVIOUS THERAPY	NO. OF PATIENTS	MEAN DURATION OF ILLNESS days	MEAN WHITE CELL COUNT x10 <sup>4</sup>	CASE MORTALITY* %
1936-37:				
None	21 <sup>1</sup>	4.1	20.4	22.9
Sulfonamides	—	—	—	—
Penicillin	—	—	—	—
Other medication	39	5.8	20.3	20.6
1940-41:				
None	352	3.5	17.5	4.5
Sulfonamides	11	5.8	18.3	0
Penicillin	—	—	—	—
Other medication	66	4.1	17.2	11.1
1945-46:				
None	217	4.5	14.4	5.4
Sulfonamides	29	6.2	11.4	6.1
Penicillin	4	—	—	—
Other medication	62	4.0	13.8	5.2

\*Corrected by exclusion of patients who died within twenty-four hours.

sponding percentages were 31.4 and 20.7. During the decade there have been no changes in organization, procedure, or laboratory personnel that might have been responsible for the changes reported in white-cell counts. A study of the duration of illness prior to admission and of the possible effect of specific therapy prior to hospitalization has been made. These factors do not appear to have been significant (Table 6 and 7), nor did the influence of sulfonamide or penicillin therapy after admission to the hospital appear to have been contributory.

The possibility has been mentioned that the decline in white-cell count, as well as the retarded response to specific therapy, was due to inclusion in the group in which many cases of viroid pneumonias were studied. This possibility is not substantiated by the data in Table 8. The cases with white-cell counts between 5000 and 10,000 would be most likely to include such viroid pneumonias, but this group exhibited the same case mortality and showed

61.5 per cent, and in 1940-41, Type I, 18.9 per cent, Type II, 4.6 per cent, Type III, 13.1 per cent, Type IV, 8.9 per cent, Type V, 3.7 per cent, Type VII, 8.5 per cent, Type VIII, 10.0 per cent, Type IX, 2.7 per cent and Type X and higher, 29.6 per cent. In 1945-46, as noted above, typing of sputum cultures was not done.

Satisfactory blood cultures were obtained in approximately 65 per cent of patients with lobar pneumonia in each of the years under study (Table 8). The percentage of blood cultures reported positive was 20.5 in 1936-37, 20.6 in 1940-41 and 13.2 in 1945-46. In each year the mean white-cell count on admission of patients shown to have pneumococcemia paralleled that of the entire group (Table 8). The case mortality in patients with positive blood cultures was significantly higher than that in other patients. Study of a small group of patients having bronchopneumonia with blood cultures positive for pneumococci revealed white-cell counts and case mortality rates similar to those described above.

The type distribution of pneumococci isolated from the blood in 1936-37 and 1940-41 paralleled that observed in the sputum. In 1945-46 Type II was most often isolated, this may have been the result of the well known high invasiveness of this type, and need not reflect a high incidence of Type II among all pneumonias in this year. It is noteworthy that a positive blood culture was obtained in only 1 of the 44 patients who had received specific therapy, which in most cases was inadequate, before admission.

In the patients with pneumococemia who recovered, the duration of fever was considerably greater than that among patients with other lobar

TABLE 7 *Duration of Illness before Hospitalization in Patients with Lobar Pneumonia*

DURATION OF ILLNESS BEFORE ADMISSION	NO. OF PATIENTS	CASE MORTALITY	
		TOTAL %	CORRECTED* %
<i>days</i>			
1936-37			
1	32	31.3	29.1
2	33	27.3	17.2
3	39	15.4	10.8
4	58	25.9	17.3
5	33	39.4	31.0
6	15	33.3	33.3
7 and over	43	41.8	34.2
Not stated	8	50.0	20.0
1940-41			
1	81	4.9	2.5
2	75	4.0	2.7
3	93	7.5	3.4
4	56	8.9	3.8
5	41	4.9	0
6	16	0	0
7 and over	51	27.4	17.8
Not stated	16	50.0	33.3
1945-46			
1	54	7.4	5.7
2	42	11.9	7.5
3	52	9.6	2.1
4	42	4.8	2.4
5	26	15.4	4.4
6	11	0	0
7 and over	67	17.9	11.3
Not stated	18	33.3	20.0

\*Corrected by exclusion of patients who died within twenty-four hours of admission.

pneumonias. Again, the duration was longer in 1945-46 — 8.2 days — than in 1940-41 — 6.9 days.

The observation that even among patients with positive blood cultures the white-cell count was much lower and the decline in fever less rapid in 1945-46 than in 1940-41 serves further to eliminate the possibility that these phenomena observed in the entire group of lobar pneumonia were due to erroneous inclusion of viroid pneumonias in the latter group.

#### MEDICAL CARE AND DURATION OF ILLNESS PRIOR TO HOSPITALIZATION

The possibility was considered that the characteristics of pneumonia were modified by the widespread use in recent years of sulfonamides and of penicillin by practitioners treating the patients before admission.

The data presented in Table 6 indicate that only a minority of patients with lobar pneumonia admitted to the Philadelphia General Hospital received medication prior to admission. A history of sulfonamide therapy was obtained in only 11 cases in 1940-41 and in 29 in 1945-46. An additional 4 patients in the latter year received penicillin. Presumably because of this therapy, the patients in this group were ill longer before hospitalization. In other respects, this group did not differ notably from patients not receiving specific therapy before admission.

The mean duration of illness before admission in each year was less in patients who recovered than in those who died. Table 7 indicates that in 1940-41 and 1945-46 this difference was accounted for chiefly by the high death rate among patients who gave a history of illness of a week or more before hospitalization. Surprisingly, there was no increase in mortality with increasing duration of illness prior to admission, provided that this duration was less than a week.

#### X-RAY EXAMINATION

X-ray examination was made in 36.0 per cent of patients with lobar pneumonia in 1936-37, 43.6 per cent in 1940-41 and 85.2 per cent in 1945-46. In many cases the examinations were made in convalescence rather than on admission. Approximately half the examinations were reported to show consolidations typical of lobar pneumonia, the remainder, in most cases, disclosed resolving pneumonia. In slightly less than 5 per cent of cases, a diagnosis of lobar pneumonia was made despite x-ray reports of "patchy" or lobular pneumonia.

#### COMPLICATIONS

The frequency of septic complications fell from 7.3 per cent in 1936-37 to about 4 per cent in the years in which specific therapy was used (Table 9). Invasive pneumococci were apparently as prevalent in the lobar pneumonias of 1945-46 as in those of 1940-41, and it is noteworthy that patients with septic complications did not exhibit the low admission white-cell counts encountered in other patients. In all three years the case mortality in patients with septic complications was very high. Chronic alcoholism, presumably marked, was noted as a complication in 5 per cent of patients in each year. The group consisted predominantly of older white men. Curiously, the alcoholic patients showed no excess mortality in 1936-37 (Table 9), but in 1940-41 and 1945-46 the case mortality was proportionately many times that of the group as a whole. Severe alcoholism is seemingly a major factor in failures of specific therapy in pneumonia.

#### DISCUSSION

The case mortality of lobar pneumonia observed at the Philadelphia General Hospital fell sharply after the introduction of sulfonamides, but no further

reduction occurred after penicillin was made available. The gross mortality appeared to rise slightly in 1945-46 as compared to that in 1940-41, but this was due to the greater proportion of older patients in the more recent year. The declining proportion of young persons is indicative of a lesser incidence or severity of pneumonia among younger patients in recent years.

Two highly significant differences were noted between the patients with lobar pneumonia in

of these criteria, and roentgenologic criteria as well, for the differentiation of these two varieties of pneumonia.

The most plausible explanation for this increasingly ill defined line of demarcation between viroid and bacterial pneumonias may rest in the hypothesis suggested in 1944 by Francis<sup>4</sup> that the picture seen in atypical pneumonia represents the underlying process of most bacterial pneumonias, with the superimposed bacterial infection merely

TABLE 8. *Patients with Pneumococemia in Addition to Lobar Pneumonia*

YEAR	NO. OF PATIENTS	TYPE OF PNEUMOCOCCUS						MEAN WHITE CELL COUNT ON ADMISSION	CASE MORTALITY		MEAN DURATION OF FEVER†
		I	II	III	IV	V	VI AND HIGHER		TOTAL	CORRECTED*	
								<i>10<sup>3</sup></i>	%	%	<i>days</i>
1936-37	33	7	3	2	0		22	20.0	45.5	42.0	9.9
1940-41	59	18	3	4	9		3	18.9	25.4	21.4	6.9
1945-46	26	4	12	0	1		7	15.0	42.3	21.1	8.2

\*Corrected by exclusion of patients who died within twenty-four hours of admission.

†Among patients who recovered.

1940-41 and those in 1945-46 — a further marked decline in degree of leukocytosis on admission, and a retarded temperature response to specific therapy. These characteristics are those of viroid pneumonias, and it seemed possible that the explanation lay in the inclusion in the series by erroneous diagnosis of a considerable number of viroid cases. Detailed analysis indicates, however, that this hypothesis is not tenable. Thus, the same characteristics were exhibited in pneumonias proved to be of bacterial etiology by demonstration of pneumococemia, and patients with

modifying to greater or less degree the basic non-bacterial disease. Such an interpretation obtains support from Hodges and MacLeod's<sup>8</sup> studies on pneumococcal pneumonia in the Army, in which epidemic surges of viral infection and epidemic outbreaks of pneumococcal pneumonia were closely associated. The increasing difficulty in differentiating bacterial and viroid respiratory infections, which is now generally experienced in clinical practice and which Ziegler and his co-workers<sup>7</sup> have documented, may thus be interpreted as being the result of a recent change in the relative intensity of the under-

TABLE 9. *Influence of Complications on Case Mortality*

YEAR	TOTAL PATIENTS	TOTAL TREATED PATIENTS	PATIENTS WITH EDEMA	PATIENTS WITH MENINGITIS	PATIENTS WITH ENDOCARDITIS	PATIENTS WITH PERICARDITIS	TOTAL SYSTOLIC COMPLICATIONS*	MEAN WHITE CELL COUNT	CASE MORTALITY		ALCOHOLIC PATIENTS	CASE MORTALITY OF ALCOHOLIC PATIENTS	
									TOTAL	CORRECTED†		TOTAL	CORRECTED†
								<i>10<sup>3</sup></i>	%	%		%	%
1936-37	261	—	12 (4.6%)	2 (0.8%)	2 (0.8%)	4 (1.5%)	19 (7.3%)	19.6	32.6	35.7	13 (5.0%)	30.8	25.0
1940-41	409	—	8 (2.0%)	2 (0.5%)	4 (1.0%)	1 (0.2%)	15 (3.7%)	21.4	46.6	33.3	21 (5.1%)	38.2	27.8
1945-46	—	302	8 (2.7%)	3 (1.0%)	2 (0.7%)	2 (0.7%)	13 (4.3%)	18.1	53.8	45.4	16 (5.3%)	31.3	21.4

\*Excluding duplications.

†Corrected by exclusion of patients dying within twenty-four hours of admission.

marked leukocytosis showed the same retarded response as those with normal white-cell counts. It appears that the pneumococcal lobar pneumonias of 1945-46 altered in certain respects from the lobar pneumonias of 1940-41 and earlier. The loss of the characteristic marked leukocytosis and dramatic response to sulfonamides or penicillin deprives us of two criteria that formerly seemed most valuable in the differentiation of bacterial and viroid pneumonias. A recent study by Racker, Rose and Tumen<sup>4</sup> has similarly demonstrated the inadequacy

lying viral and superimposed bacterial infections. The changes observed in lobar pneumonia at Philadelphia General Hospital during the past decade are explicable on the hypothesis that lobar pneumonias represent a heterogeneous group that in recent years has included a larger number of patients in whose disease the bacterial factor was relatively slight.

It is noteworthy that early reports on the use of sulfonamides, as well as of specific serum therapy, emphasized the necessity for early institution of

treatment, whereas the lack of correlation between duration of illness before application of therapy and the case mortality observed in this study is suggestive of a diminishing importance of the bacterial factor

The case mortality rates of lobar pneumonia reported in England and in parts of western Europe prior to the introduction of sulfonamides were considerably lower than the high rates experienced in this country before specific drug or serum therapy was used.<sup>1, 8</sup> This may indicate that pneumococcal lobar pneumonia was not in the past a homogeneous entity and that the viral factor or the bacterial factor, or both, varied geographically

The diminishing importance of the bacterial factor need not be attributed to the influence of sulfonamides and of penicillin. The mortality from lobar pneumonia had declined sharply between 1925 and 1937, to a far greater degree than could have been due to the limited use of serum therapy.<sup>1</sup> As in tuberculosis the decline in pneumonia cannot be explained wholly by the therapeutic advances that have been made, and probably the changes in both diseases are due not to modification of the virulence of bacteria, but to constitutional and environmental factors affecting host resistance

The marked increase in case mortality with age deserves emphasis, for special attention to this factor is required in any evaluation of therapeutic trials in pneumonia. The strikingly low case mortality (less than 1 per cent in lobar pneumonia reported in the Army<sup>9</sup> and the Navy<sup>10</sup>), during the war years is not likely to be duplicated in the general population

The high rates among patients over the age of fifty noted in recent reports from the Cook County Hospital<sup>11</sup> and the Gallinger Hospital,<sup>12</sup> as well as in the present study, and the high rates still observed in patients with alcoholism, empyema, meningitis, endocarditis and pericarditis indicate that the therapeutic problems of pneumonia are not completely solved

#### SUMMARY

A study has been made of lobar pneumonia at the Philadelphia General Hospital in 1936-37, a year in which specific therapy was not employed, in 1940-41, a year in which sulfonamides were generally

applied, and in 1945-46, a year in which penicillin was available as an adjuvant to the sulfonamides. The case mortality rates were 23.3 per cent, 5.4 per cent and 6.5 per cent for the three years, the apparent slight increase in the last year being due to a striking rise in age of the patients

Although the mortality of lobar pneumonia did not vary significantly between 1940-41 and 1945-46, highly significant differences between these years were observed in two respects: a reduction in white-cell counts on admission and a retarded temperature response to specific therapy. Detailed analysis indicates that these changes cannot be attributed to erroneous inclusion in the 1945-46 series of large numbers of viroid pneumonias

It is concluded that pneumococcal lobar pneumonia as observed in 1945-46 had altered significantly from the disease encountered in previous years, and in such fashion that it was clinically difficult to distinguish from viroid pneumonias. It is suggested that lobar pneumonia is not, and has not been, a homogeneous entity but represents rather an underlying viral process modified to greater or less degree by superimposed bacterial infection. The relative importance of the viral and bacterial factors in lobar pneumonia appears to have altered in recent years

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## PRINCIPLES OF THE MASSACHUSETTS MEDICAL SOCIETY\*

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THE concept of this symposium came from the late Dr. Michael A. Tighe. He believed that it was time we told each other and the people of the Commonwealth where we are now and where and how we are going.

The following are the principles of the Massachusetts Medical Society as developed by the Subcommittee on Medical Economics and adopted by the Council about a year and a half ago.

The objective of adequate medical care in our free society is to make available to everyone — regardless of race, color, creed, financial status or place of residence — every known essential preventive, diagnostic and curative medical service of high quality. The attainment of such medical care must necessarily be an evolutionary process which will require the co-operation of all concerned over a period of years.

The success of any plan for medical care is dependent on the mutual co-operation of the public, those rendering professional services and the administrative agencies. This co-operation can be obtained only if those rendering the services are convinced that they will have a continuing authoritative voice in the formulation and execution of policies and plans, thereby assuming their proper share of responsibility.

Provision of adequate medical care for those unable to obtain it by voluntary prepayment plans or by direct payment is the responsibility of the local or state government. Part of the burden of this responsibility may be assumed by charitable agencies. Federal grant in-aid to state programs administered by state boards of health is an acceptable method of helping to meet this responsibility.

The medical care of those who are able to purchase it by voluntary prepayment plans or by direct payment is the responsibility of the individual.

Eligibility for receiving benefits under a program aided by federal grants should be determined by the individual states.

The patient shall have free choice of his physician group of physicians, clinic or hospital from among those participating in any plan provided that the physician group of physicians, clinic or hospital shall have the right to refuse or to accept the patient.

Physicians and other qualified persons rendering medical care shall receive adequate remuneration for their services.

The physician shall be free to elect or reject without prejudice participation in a medical-care plan. The rights of the physician as to the choice of methods by which he is to be paid shall be fully protected.

The Massachusetts Medical Society looks upon these basic principles as essential to the development of any successful medical-care plan and, as guides by which to evaluate medical-care plans that may be proposed in the future, with the understanding that changing conditions may require their later revision.

I remember a number of years ago when we, in the Committee of Public Relations, under the able leadership of Dr. Ernest L. Hunt, made some spot studies in adequacy of medical care in this state. I remember in that same committee when Dr. Nathaniel W. Faxon discussed prepayment hospitalization, he stated that such a plan would not

be started without our approval and would proceed only with our approval. I remember that in that same committee discussion of medical-care plans later developed and that, under the brilliant and aggressive leadership of Dr. James C. McCann, the Blue Shield was conceived and launched. At about the same time the White Cross was born. This was an experiment in medical care sponsored by men who were impatient with such "inadequate" concepts for solution of problems in medical-care distribution as the Blue Shield then seemed to them. I have always thought that these men could have performed a service by reporting on the causes of failure factually and objectively.

You will hear today where Blue Cross and Blue Shield stand now. I think that Massachusetts can be proud of its progress in trying to satisfy unmet needs in medical-care distribution. Social changes properly proceed slowly and safely, not at a speed that would satisfy the impatient reformers who blueprint Wagner-Murray-Dingell bills, but fast enough to arouse protests from the ultraconservatives.

The next five years, the next one or two years and perhaps the next few months will be crucial. Change is needed, and with a properly statesmanlike attitude we can provide leadership that will continue to earn us the respect and confidence of a people who have a right to expect leadership from us because we are specialists in the field.

Let us consider casually some of the factors that must be borne in mind as we proceed toward adequate medical care for all the people.

\* \* \*

When we consider adequacy of medical care for all regardless of economic status, we must recognize that there is more involved than rhetoric. Cost is not the chief barrier to utilization of available medical care. For years the Commonwealth has had cancer clinics accessible to all the people that make it entirely unnecessary for anyone to be hoist for long to unrecognized cancer. People still have symptoms for an average of about four months before they seek medical care. There is a great deal in the field of preventive medicine — for example, in tuberculosis and venereal disease — that could be practically eliminated if people would use the facilities for diagnosis and care that are now available. Progress is being made all the time, of course, and the Massachusetts Medical Society is continually doing a great deal toward helping to get medical care of a better quality to the consumer.

\*Presented at the annual meeting of the Massachusetts Medical Society Boston May 30, 1947.

†Formerly president of the Massachusetts Medical Society.

I am very sure that if there were more and better district health councils throughout the Commonwealth tremendous strides would result. The district health council is an organization consisting of representatives of all the facilities and agencies concerned in the distribution of medical care, such as the doctors, the hospitals, the nurses, the druggists, the dentists, the public-health administrators and the social workers. These organizations could analyze the available facilities and see that there is more adequate utilization of those existing, and also supplement these by assisting in the development of services that are deficient.

There is a great need for more utilization of dentists. In England, where government insurance has been in effect for many years, of the 14,000,000 people eligible for dental care, only 7 per cent avail themselves of the service. Massachusetts is still one of the states whose populations have the poorest teeth in the country in spite of a relatively low cost barrier. Very recently Navy medical officers conducted studies of housing, sanitation and health of our coal miners and found conditions that were not satisfactory. These people need better facilities but particularly more education in living standards. Deficiencies even in such fundamentals as running water and indoor toilets exist to a surprising degree. The metropolitan health survey found very recently that there were 100,000 people living in Washington, D. C., without these facilities.

Some planners who sit in ivory towers think that all medical care should be dispensed by groups. There are plenty of good reasons why more group practice should be carried on, but that will develop better by evolution—through trial and error. Groups were more popular for a while after World War I, but there were many failures and only a few brilliant successes. Time does not permit analysis of the causes of failure. The general practitioner is the backbone of the system of distribution of medical care to the people, and I hope that he always will be. I am willing to debate this with anyone who does not agree. The general practitioner is as essential to medicine as the infantryman is to the army. Every general practitioner has his own informally organized group. He knows who among those available is the best qualified for the patients who need a specialist. It is only relatively few who need specialized diagnostic care or treatment. It is not good economy to consult the specialist for everything. There is a degree of obligation in organized groups to utilize only group personnel. This limits choice too much in some cases.

There are a group of people—the medical indigents—who are able to meet the expenses of ordinary medical care but once in a few years are confronted by unusual diagnostic costs and perhaps surgery and hospitalization. These people vary in number with the degree of prosperity in the country. But they are enough of a problem so that it seems

probable that ultimately the only logical way to meet the cost is by governmental subsidy. Many of those who would have been medically indigent have been lifted out of that group by being able to pay for medical care through Blue Cross and Blue Shield. I have patients who were formerly unable to pay for obstetric care and are now proud that they can meet these costs in this way. I have figures that indicate that in a one-hundred bed hospital the doctors on the ward services contribute more than \$100,000 a year in medical and surgical services to the community. We have done very little complaining about this. Many people think that we are paid a salary for these services.

The Taft Bill (S 545) proposes to have the federal Government subsidize the state to take over this burden. It would be essential to have a continuing authoritative voice given to the doctors in the management of the professional side of such a plan. In England, under a new plan, the Labor Government has taken over medicine and the hospitals lock, stock and barrel. The importance of proper technical advice from the doctors has not been realized. There is an advisory board, but it has been given no power, one of the medical statesmen of England recently said, "You know that kind of a board can cut no ice." The Massachusetts Department of Public Health appreciates the necessity of co-operation with technical advisory boards. The Department of Public Welfare is beginning to learn. Federal financing means that the federal Government will need to raise the money, federal money comes from the taxpayers, and Massachusetts pays a good share of federal taxes. We approve of the principle of taxing Massachusetts more to provide for some of the poorer states—in the same way that we who are better able to bear the tax burden take care of the poor in our own town.

The physician should receive adequate remuneration for his services. The cost to the medical schools for education is about \$2400 per year per student. One New England school a few years ago had \$5000 in the budget per medical student per year. Dr. Elliott P. Joslin states that the average doctor in the Commonwealth practices only fifteen years. The man or woman who goes to college for four years and to medical school for four years has to spend at least \$10,000 of somebody's money for his education. Then he has from two to five years' training in a hospital before he begins to pay off the mortgage. He has barely time to get a proper basis for living for his family and enough insurance to keep them from becoming public charges before his years of usefulness are waning. Certainly, those who know the facts do not expect the doctor to do the job he does for less money.

The Massachusetts Medical Society has a few leaders who have constantly tried to discover and meet the medical needs of the Commonwealth and

of the country. As we come into these times of more active social adjustment we have made very considerable strides in better organizing ourselves to serve the people. We might have done a good deal more in the past, but too many of us have been too busy meeting the needs on the firing line, moreover,

social changes develop along sounder lines if the whole body politic has a chance to get conditioned to change at an evolutionary rate. It is axiomatic that the best that is known is ahead of the best that is done in this as in all fields.

281 Main Street

## WHO CARES FOR THE EPILEPTIC?\*

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**E**PILEPSY is a larger public-health problem than is generally realized, even by doctors. Its supposed infrequency is due to the practice of concealment and to the widespread popular belief that for epilepsy there is no effective treatment. The United States Selective Service figures of 1917 gave for Massachusetts an incidence of 0.59 per cent (as compared with 0.515 for the whole country). Yet medical officers know that thousands of epileptic patients were not detected by the Selective Service examinations, thousands risked a lie to risk a life for their country (and the esteem of their fellows). If the statistics are accepted, epilepsy is as common as active tuberculosis, diabetes or crippling infantile paralysis.

In Massachusetts, how many epileptic patients are supervised medically? How many are cared for in clinics, and how many in private offices? How is the burden distributed among practitioners and the various specialists? Do physicians wish for additional information about epilepsy and newer methods of therapy? In the summer of 1946 the Committee on Public Health of the Massachusetts Medical Society, which is commissioned by the Society to "foster the knowledge of disease by any appropriate measures," sent a letter to each member of the Society asking for information that would help to answer these questions. The American Epilepsy League inspired the effort. Expenses were met by the Bay State Society for the Crippled and Handicapped, which helps to support the Seizure Unit of the Children's Hospital of Boston. Letters went to 5539 physicians. Of these, 2997, or 54 per cent replied to either the first or a follow-up letter. Deducting 201 replies from men who were in, or just out of, service, 2796 blanks remained.

### Patient Load

The questionnaire asked for the number of epileptic patients who had been seen privately or in

clinic during the previous twelve months. Of the physicians replying, 1613, or 58 per cent, had "seen" epileptic patients in the past year, and 1183, or 42 per cent, had not. Of the 1613 doctors who treated these patients, 1472, or 91 per cent, did so in private offices, and 316, or 19 per cent, in a clinic. Ten per cent saw patients in both places.

Doctors were asked the approximate number of epileptic patients seen in the year. 11,434 patients were reported, of whom 60 per cent were office and 40 per cent were clinic cases. This does not include 2746 patients cared for in institutions. The numbers are exaggerated because a given patient may have visited more than one physician or may have been seen both as a clinic and as a private patient.

### Distribution of Patient Load

The 1472 doctors who reported office treatment of epileptic patients during the year saw a total of 6905 patients, or an average of 4.7 each. The much smaller number of doctors, 316, saw a total of 4529 patients in a clinic—an average of 14.3 per doctor. If the total number of noninstitutional ("extra-mural") patients are divided equally among the doctors who treated patients, the number per doctor is 7.1, of which 4.3 are office and 2.8 clinic cases. If the 11,434 patients are divided among the 2796 "active" doctors answering the questionnaire, the distribution is 2.5 office and 1.6 clinic, with a total of 4.1 patients. Probably each physician who returned the questionnaire treated more epileptic patients than those who consigned it to the wastebasket. Assuming that the 46 per cent of doctors who did not return the questionnaire saw only half as many of these patients as those who did, the stated number of epileptic patients, on the basis of equal distribution among the 5338 physicians, provides each with three patients. This number is undoubtedly too high because of duplication. Patients reported by the heads of x-ray departments and other laboratories were eliminated because they would have been reported also by the referring physician, but other duplications could not be detected without a request for the names of patients. The incidence of epilepsy among men examined for

\*From the Children's and Infants' Hospital.  
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the Army in 1917 would give Massachusetts approximately 20,000 epileptic patients, or something like 4 patients to each doctor. Probably not more than half this number were seen by the doctors in Massachusetts during the year in question. This conclusion will not surprise those who examined Selective Service registrants in the last war. Many acknowledged patients had not consulted a physi-

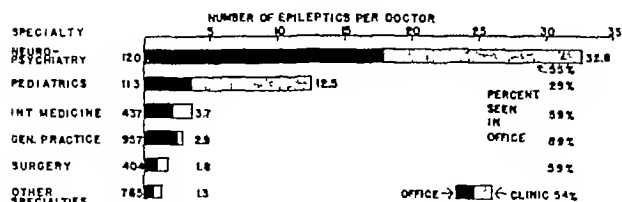


FIGURE 1 Number of Epileptic Patients Seen for Each Doctor Answering the Questionnaire

Neuropsychiatry includes neurosurgery. The figures at the left refer to the number of doctors. The solid portions of columns refer to office, and the dotted portions to clinic patients. The percentage figures at the right give the proportion of all patients seen in the office.

cian, believing that doctors could offer no effective treatment.

### Patient Load and the Specialties

Physicians were asked to name their specialty. The number of patients treated annually by practitioners and various specialists is shown in Figure 1. As would be expected, the group of neurologists,

groups presented in Figure 1, all but two saw a little more than half of the epileptic patients privately (from 54 to 59 per cent). The two groups that were far outside this zone were the general

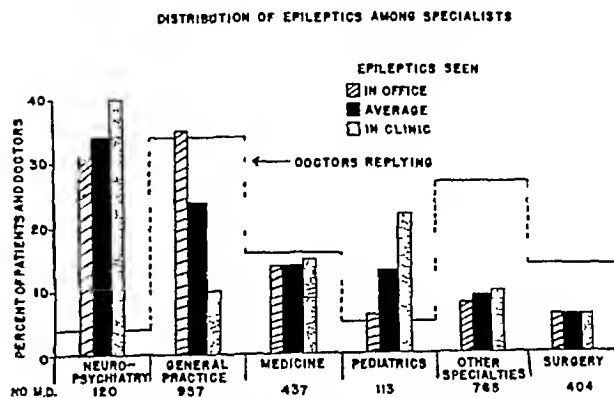


FIGURE 2 Distribution of Epileptic Patients among Groups of Doctors

The columns represent the proportion of the total of 11,434 patients who were seen by the specified doctors. The horizontal lines give the proportion of the total of 2796 doctors who belong to each specialty. The hatched columns represent patients seen privately, and the dotted columns those seen in clinics.

practitioners, with 89 per cent office patients, and the pediatricians, with only 29 per cent of patients seen in the office and 71 per cent seen in clinics. Since clinic work carries little or no monetary reward, pediatricians must be carrying a disproportionate share of the charity load. Whether this

TABLE 1 Distribution of Office and Clinic Patients among Various Groups of Doctors

SPECIALTY	DOCTORS		PATIENTS SEEN IN OFFICE		PATIENTS SEEN IN CLINICS		ALL EPILEPTIC PATIENTS	
	NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE
Neuropsychiatry	120	4	2,148	31	1,797	40	3,945	34.5
General practice	957	34	2,454	35	311	7	2,765	24.2
Medicine	437	16	937	14	661	15	1,598	14.0
Pediatrics	113	5	412	6	1,000	22	1,412	12.3
Other specialties	765	27	533	8	469	10	1,002	8.8
Surgery	404	14	421	6	291	6	712	6.2
Totals	2,796		6,905		4,529		11,434	

psychiatrists and neurosurgeons heads the list, with an average of 32.8 patients per doctor (the five neurosurgeons who reported had an average load of 68 patients). Next in importance are the pediatricians, who saw an average of 12.5 epileptic patients. Aside from these two groups—numbering only 233 doctors—the internists, general practitioners, surgeons and other specialists saw, respectively, from 3.7 to 1.3 such patients in the year.

In view of the present agitation for lower cost of group treatment of patients, comparison of the numbers of patients treated as private and as clinic patients deserves special attention. Of the six

preference of the parents of the epileptic child for the clinic is due to economic conditions or to a belief as a result of publicity that better treatment can be obtained in the clinic is not clear from this survey. The survey of pediatric service now going forward should demonstrate whether other diseases of children tend to receive care in clinics at the expense of office practice.

The preceding data may give the impression that the care of epileptic patients is in the hands of neuropsychiatrists and pediatricians. Study of the share of each specialty in carrying the total patient load demonstrates the incorrectness of this view.

Neuropsychiatrists, neurosurgeons and pediatricians treated only 37 per cent of office and 47 per cent of all patients. This is because these specialties constitute only 9 per cent of the doctors who responded to the questionnaire. The essential data are presented in Table 1. The columns of Figure 2 represent the distribution of extramural patients among the six groups of doctors, and the horizontal lines indicate the distribution of the doctors themselves. Thus, at the left of the figure, neuropsychiatrists number but 4 per cent of the number of doctors replying, but they saw 34.5 per cent of the 11,185 patients reported and, although each treated fewer clinic than office patients (Fig. 1), they saw a larger proportion of the total clinic cases than of the total office patients. The general practitioners carry the next largest load — namely, 35 per cent of office and 24 per cent of all patients. Practitioners and internists combined saw approximately half (49 per cent) of all office patients. The neuropsychiatrists and pediatricians combined saw 62 per cent of clinic patients. A comparison of the height of columns and of the solid line in Figure 2 displays the proportion of patients seen by various groups of doctors in relation to the numbers of doctors in these groups. Thus, neuropsychiatrists and pediatricians saw a large proportion of patients in relation to their own meager numbers. Surgeons, practitioners in clinics and other specialists saw relatively few epileptic patients. This tabulation, like that of Figure 1, emphasizes the relatively large clinic load carried by pediatricians. They receive relatively small recompense for the work of this nature that they do. As would be expected, various specialties such as the eye, ear, nose and throat, orthopedic and skin take care of relatively few patients with epilepsy.

#### *Physician Interest in Newer Knowledge*

The degree of mistreatment of a given patient is measured by how far the given therapy falls short of utilizing the best possible methods. On each accession of knowledge a previously "good" form of therapy becomes mistreatment, or at least inadequate. The same statement is as true of social as of drug therapy. For many centuries effective medical and surgical therapy was nil. Discoveries of the last ten or twelve years mean as much for the present-day epileptic person as the discovery of ether meant to the surgical patient a century ago. Yet, as neurologists of the Selective Service boards who questioned the raw mass of young men can testify, many patients with the Hippocratic disease either receive no care or treatment little better than that prescribed by Hippocrates himself. Massachusetts may be called the home of electroencephalography, of modern anticonvulsive therapy, or research and of interest in the disorder. Massachusetts has facilities for the care of epileptic patients unequalled elsewhere: the headquarters of

the International League Against Epilepsy and of the American Epilepsy League, a dozen electroencephalograph laboratories, the Monson State Hospital, a national center for treatment and research at the Cushing Veterans Administration Hospital and special clinics for epilepsy in several hospitals. Unfortunately, facilities are too much concentrated in Boston. The New England Epilepsy League hopes to learn of physicians in New England who are both interested and competent in handling epileptic patients. The diagnostic, research and training center recently established at the Children's Hospital in Boston with the aid of the Bay State Society for the Crippled and Handicapped plans an extension of its services to physicians, hospitals and social agencies throughout the Commonwealth. Like charity, the application of medical knowledge does not always begin at home, and probably only a minority of the epileptic patients of Massachusetts are today receiving adequate medical and social care.

Social therapy is even more antiquated than medical. Twenty-six per cent of the colleges and universities of New England have a blanket rule against admission of scholastically qualified but epileptic students, the great and good Massachusetts General Hospital, birthplace of medical social service, will not engage a person who has a history of seizures, and the great Commonwealth of Massachusetts with a law that allows a handicapped worker to waive his rights to accident compensation will not extend that privilege to epileptic patients, nor will it permit the physician to give contraceptive advice to his epileptic patient who wants marriage but not children. Fourteen states of the Union forbid the epileptic person to marry, and the United States Government subjects the epileptic patient who comes to this country for medical advice to an embarrassing delay on Ellis Island.

To meet the need of doctors, social agencies and patients for up-to-date information about epilepsy and its medical and social therapy, the American Epilepsy League has assembled a series of medical reprints and popular articles, as well as several books. With the original questionnaire went a list of twelve of these articles and several books. Physicians were asked to check those desired. Of the 785 doctors who answered the first letter, 578, or 73 per cent, requested one or more reprints. The proportion was 80 per cent of the 434 doctors who saw patients, and 58 per cent of the 144 doctors who did not. These 578 doctors asked for three thousand, two hundred and thirty-three pieces of literature, or 5.6 per doctor. This average number was 5.9 for doctors who saw epileptic patients and 4.5 for those who did not. Of all articles requested, 73 per cent were technical, and 27 per cent popular — for the benefit of patients and their friends and relatives.

## SUMMARY

Backed by the Committee on Public Health of the Massachusetts Medical Society and the Bay State Society for the Crippled and Handicapped, the American Epilepsy League sent questionnaires to all members of the Medical Society. Of 2796 doctors replying, 58 per cent had treated epileptic patients during the previous year. Of these, 91 per cent saw them in the office, 19 per cent in the clinic, and 10 per cent in both office and clinic. Of the 11,434 patients treated, 40 per cent were clinic and 60 per cent were office patients. Equally distributed, there would be 41 patients for each doctor who returned the questionnaire. Taking into account the duplication in this survey, probably not more than half the estimated 20,000 epileptic persons in Massachusetts are receiving active medical supervision.

Among all doctors replying, the average neuropsychiatrist or neurosurgeon saw 33 patients, the pediatrician 12, and other specialists and general

practitioners from 37 to 17 each. Pediatricians treated 71 per cent of their epileptic patients in clinics, whereas all other doctors saw only 33 per cent there. Of all epileptic patients treated privately, the general practitioner saw the largest proportion—35 per cent, 31 per cent were seen by neuropsychiatrists, and 14 per cent by internists. Of all clinic patients, 40 per cent were seen by neuropsychiatrists, 22 per cent by pediatricians and 15 per cent by internists. Pediatricians constituted only 5 per cent of the doctors who reported, but they treated 22 per cent of all clinic patients. They bear an unusually heavy load of charity patients. Of the 785 doctors who responded to the first questionnaire, 73 per cent requested reprints of articles on epilepsy, of which 73 per cent were technical in nature. Study of the questionnaires returned, together with our general experience, convinces us that both medical and social treatment of epileptic persons in Massachusetts and other states falls far short of utilizing knowledge gained during the past dozen years.

## A STUDY OF VIRUS CARRIERS FROM A POLIOMYELITIS OUTBREAK AT A BOYS' CAMP\*

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**S**MALL, localized outbreaks of poliomyelitis offer unusual opportunities for epidemiologic study. The more isolated the population unit under observation, the less complex appears the task of tracing chains of infection. However, it remains for future discoveries to determine how true this may actually be so far as poliomyelitis is concerned.

A recent outbreak of poliomyelitis in a boy-scout camp in western Massachusetts seemed to be particularly well suited for epidemiologic study. In the first place, prior to its occurrence, no cases of infantile paralysis had been reported from all of western Massachusetts for three months. Furthermore, the location of the camp near the summit of an isolated mountain reservation reduced the opportunity for outside contact of campers and personnel, although the camp cannot be described as a truly "isolated community."

Investigation of this outbreak was instituted after the rather sudden occurrence of 3 cases at the camp in July, 1946, when it was decided to disband the organization. Nearly all personnel returned home, with the exception of 20 persons who, for one reason or another, remained behind. Those events are presented graphically in Figure 1.

The plan of the study was to determine the carrier rate in the group of campers who were most heavily exposed to, or perhaps together with, known cases, as measured by virus isolations from throat and stool cultures.

It was believed that a number of features could be learned from this approach. Recent investigations have demonstrated that the poliomyelitis virus may be isolated more readily from stools than from material obtained from the oropharynx of patients<sup>1</sup>, however, observations on the relative frequency of intestinal as opposed to throat carriers among healthy contacts are few in number<sup>2,3</sup>. It was proposed in this study to compare unpooled serial specimens (throat swabs and stools) obtained from contacts over a period of several weeks. Furthermore, since it is not known how often healthy carriers may directly transmit virus to others, investigation of children in households to which exposed campers

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returned also presented a limited opportunity to acquire new data on this point

### MATERIAL AND METHODS

The camp in western Massachusetts is referred to as Camp Pfd. Since all the clinical cases of poliomyelitis appeared in one of three groups of campers, it was decided to develop the laboratory investigation with this one group as the focal point. Because the camp had been dispersed at the time the study was begun, the aid of the local health department and visiting nurses\* was sought in obtaining laboratory specimens. From the time of the out-

The blood was centrifuged, usually on the day of collection (or within twenty-four hours during which it was kept in the icebox). Serum was drawn off and frozen †. All material was kept frozen, even during transport to New Haven, until it was prepared for animal inoculation or testing.

**Virus testing.** In general the methods followed have been described in previous communications from this laboratory.<sup>1,4,6</sup> Throat specimens were prepared for intracerebral inoculation by elution from the swabs and subsequent etherization.<sup>6</sup> Stools were also inoculated intracerebrally after their processing in the ultracentrifuge.<sup>4</sup> Rhesus (*Macaca*

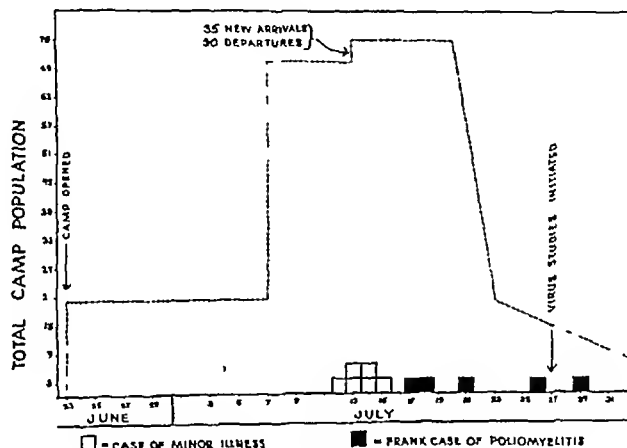


FIGURE 1 Occurrence of Clinical Poliomyelitis at Camp Pfd in Relation to Camp Population.

break, throat swabs and stool samples were obtained three times a week for four weeks from 18 of the 26 members of this group. Whenever possible, similar specimens were also taken from children in households to which exposed campers had returned. For serologic studies, each of the selected group of campers and their household contacts was subjected to three bleedings, one at the time of the initial visit and two others at intervals of three weeks. Blood, throat and stool specimens were also obtained from 7 other campers who were not members of the group in which the clinical cases occurred.

Throat swabs were placed in 1 cc. of water in a dusteroid tube and frozen immediately after being obtained. Stools were also frozen as soon as they were collected by the health-department personnel.

\*Misses Ann M. Thompson, R.N., Charlotte Cornwell, R.N., Beulah Zilling, R.N., and Justine Baldissarotto, R.N., helped in the collection of these specimens.

*mulatta*) monkeys were used as test animals — as a rule, one monkey being utilized for each test. All positive results for virus were confirmed by histologic findings of typical lesions in the spinal cords.

**Neutralization tests.** These were carried out with the Lansing and Y-SK murine-adapted, monkey-pathogenic strains of poliomyelitis virus. The technic was similar to that outlined by the Commission on Neurotropic Virus Diseases of the Army Epidemiological Board,<sup>7</sup> constant amounts of virus being used with varying dilutions of serum.

### EPIDEMIOLOGY

The camp grounds covered an area of several acres and were located near the summit of a mountain (elevation, 1930 feet) in Berkshire County,

†We are indebted to Dr. H. Lee M. Scoville, House of Mercy Hospital, Pittsfield, for her aid in preparing the serum.

Massachusetts Tents were placed in three areas, each about 50 yards in diameter and 100 yards from each other. Another section of the camp site was set aside for a screened kitchen cabin, unscreened mess and utility tents, an infirmary, several odd cabins and tents occupied by members of the staff. Swimming and water sports were carried on in a fresh-water lake several acres in extent, located below the level of the rest of the camp.

The personnel of the camp was divided generally into four groups, three of campers (Rangers, Pioneers and Blue Moccasins) and one staff group. The ages of the campers ranged from twelve to eighteen

TABLE 1 *Date of Arrival and Onset of Cases*

CASE No	DATE OF ARRIVAL AT CAMP	DATE OF ONSET
1	July 7	July 17
2	July 7	July 18
3	June 23	July 21
4	June 30	July 26
5	July 7	July 29

years. There was no sharp division regarding home town or date of arrival at camp.

Sports and the daily routine were carried on by groups. However, on occasion all campers participated in general activities. Meals were eaten by all campers and the staff simultaneously in a common dining room, but each of the groups ate at a separate table. Although all the food from the camp kitchen was distributed equally among the three groups of campers, some additional food was brought in on Sundays by relatives and friends. This food was generally distributed by campers only to members of their own group. This was but one of the indications that in spite of the isolated location, the community was in close touch with the outside world.

The Ranger and Pioneer groups were housed in large tents, 8 campers being assigned to each tent. The leaders and counselors for each of these groups were in two-man tents. The campers and counselors of the Blue Moccasin group were housed in seventeen tents, each tent housing 2 persons. Sewage disposal was by pipe and pit urinals and by pit latrines covered with unscreened boxes. Garbage was carried away from the camp grounds and disposed of. The milk was pasteurized and of good quality, and arrived in 40-gallon cans. At mealtime the milk was poured into pitchers for individual tables. The food was obtained from recognized sources, and all perishable foods were kept on ice. The water supply came from a tubular well, and tests revealed it to be free from bacterial contamination.

The first group of about 20 persons, consisting of staff members, counselors and junior leaders, arrived in camp on June 23, 1946 (see Fig 1). The first contingent of campers, comprising more than

50 boys arrived on July 7, when some of the first group returned home. A third group of approximately 35 campers arrived on July 13, when 30 of the original campers went home. With the exception of 20 persons, all personnel returned home between July 20 and 23.

According to the infirmary records, between July 12 and 16 there occurred 6 cases of minor illnesses in which the diagnosis was indefinite but the signs and symptoms were compatible with suspected (abortive) poliomyelitis. Although this diagnosis was not considered at the time, the patients were seen to be ill by the camp nurse. There were two small epidemics of diarrhea, primarily among the Pioneer group during the first two weeks of camp, and, in addition, a number of upper respiratory infections involving about 30 per cent of the camp population throughout the entire time of its operation.

The distribution of cases of infantile paralysis, according to the day of onset and the time of arrival at camp of each patient, is shown in Table 1. Cases 1, 2 and 5 had arrived in camp on July 7, and Cases 3 and 4 on June 23 and 30 respectively. They all became ill between July 17 and 29.

As stated above, all 5 cases occurred among 31 boys who were members of one group, the Blue Moccasin group, between July 7 and 14. Cases 1 and 5 were tent mates, both boys lived in the same town, Great Barrington. Patients 2, 3 and 4 resided in Pittsfield, another nearby town. No cases of infantile paralysis had been reported from either community since 1945. Not a single member of either the Pioneer or the Ranger group developed clinical poliomyelitis. Of the 5 cases, a diagnosis of bulbar poliomyelitis was made in 4. One patient died because of involvement of the respiratory center, and another received care in a respirator for a period of several months.

#### RESULTS OF LABORATORY INVESTIGATION

##### *Establishment of the Strain of Virus and Attempt at Identification*

The strain was first isolated readily from the pooled fecal specimens obtained from 3 of the hospitalized patients (Mo, He and La). Three serial passages of the virus in monkeys were carried out, and attempts were made with central-nervous-system material from each monkey passage, as well as with infective human stools, to adapt the virus to mice and cotton rats. Whereas the strain took easily in monkeys, no evidence of disease was seen in the rodents, even when such technics as concentration in the ultracentrifuge,<sup>8</sup> blind passage and Milzer's autolyzed brain method<sup>9</sup> were used.

Although the Pfd camp strain has not proved to be pathogenic for rodents, attempts were made to determine whether it was related immunologically to the Lansing and Y-SK strains. Convalescent and

hyperimmune monkey serums were prepared for the camp strain, and neither serum neutralized Lansing or the Y-SK strain.

Thus, the Pfd strain of virus appears to be typical of the usual type in the experimental disease produced in monkeys and in its failure to take in rodents. Moreover, no relation was demonstrated between this strain and the Lansing and Y-SK strains. These strains were both isolated several years ago, the former from the brain of a fatal case in Lansing, Michigan,<sup>10</sup> in 1938, and the latter from the stool of an abortive case in New Haven, Connecticut,<sup>11</sup> in 1937.

### Carrier Rate among Campers

An attempt was made to determine the carrier rate among the healthy members of the Blue Moc-

TABLE 2. Presence of Virus in Stools and Throat Swabs

Source	JULY 27- AUGUST 2 COLLECTION		AUGUST 5-14 COLLECTION		AUGUST 16-23 COLLECTION	
	STOOL	THROAT	STOOL	THROAT	STOOL	THROAT
<b>Patients:</b>						
Fi	+	+				
Mo.						
La.						
Ho.	+					
ML						
<b>Healthy Blue Moccasin group:</b>						
Be.	-	-			-	-
Dr.	-	-			+	-
Da.	-	-	+	-	-	-
Ha.	-	-			-	-
Rj.	-	-			-	-
Sy.	-	-			-	-
TL	-	-			-	-
Ah.	-	-			-	-
Ch.	-	-			-	-
Co.	-	-			+	-
De.	-	-			-	-
Ev.	-	-			-	-
Fe.	-	-			-	-
Pe.	-	-			-	-
Pow.	-	-			-	-
Wa.	+	-			-	-
Pa.	-	-			-	-
<b>Home contacts of healthy carriers:</b>						
M. Dr.	-	-	-	-	-	-
J. Cu.	-	-	-	-	-	-
<b>Remote contact campers:</b>						
La.	-	-				
Or.	-	-				
Re.	-	-				
Cna.	-	-				
Ja.	-	-				
C.	-	-				
Le.	-	-				

casin group. It may be assumed that the latter campers had the same opportunity for exposure as those who developed poliomyelitis. There had, of course, been contact between them. These data are presented in Table 2.

One of this group from whom specimens were collected developed the first symptoms of poliomyelitis one day after the first collection of samples. Both the stool sample and the throat swab collected at this time from this boy (Fi) contained poliomyelitis virus.

Of the remaining members of the group, 5 virus carriers were found among 18 boys tested. All 5 were intestinal carriers, and only 1 of the 5 was

found to harbor virus in the throat. None of them gave a history of symptoms compatible with the picture of mild poliomyelitis.

Of these 5 carriers, 3 were found to be excreting virus in the stools for a period of at least three or four weeks. Whereas the patient (Cu) who was both a throat and intestinal carrier excreted virus in the stool for about a month, virus could no longer be found in the throat after the first week. These

TABLE 3. Humoral Neutralizing Antibodies to Lansing and Y-SK Strains in 3 Healthy Carriers of Virus and in 3 Healthy Controls Found Not to Be Carriers of Virus

Source Carriers of virus:	SERUM ANTIBODY*		
	7/30/46	8/22/46	9/11/46
A	+	++	+++
B	+	+	++
C	+	+	++
<b>Noncarriers of virus</b>			
D	++	++	++
E	-	-	-
F	-	-	-

\* — = No demonstrable antibodies.  
+ = Unadiluted serum neutralized virus.  
++ = 10x diluted serum neutralized virus.  
+++ = 100x diluted serum neutralized virus.  
The amounts of virus used in these tests varied from 10 to 100 I.D.<sub>50</sub> doses.

findings are analogous to those encountered in similar studies on the frequency and duration of virus carriers among patients with clinical poliomyelitis<sup>1</sup> and in a similar camp group of healthy contacts.<sup>2</sup>

A small control group of 7 Pfd campers, not belonging to the Blue Moccasin group, were also tested. No intestinal carriers were found among them.

### Carrier Rate among Secondary Contacts

Since the camp was officially closed and the boys sent home soon after cases occurred at the camp, an opportunity existed for studying secondary familial contacts, especially those of virus carriers.

Of the 5 healthy carriers, only 2 had siblings at home. Throat swabs and stools from both these siblings were collected over a period of a month. None of this material contained virus. It is of interest that one of these secondary contacts was exposed to a carrier harboring virus in the throat as well as in the intestinal tract.

### Antibody Response to Murine-Adapted Strains of Virus

Although the Pfd strain did not appear to be related to the Lansing or Y-SK murine-adapted strains, neutralization tests in mice were carried out with the latter strains on serums from campers representing 3 healthy carriers of virus and 3 healthy controls who had been found not to be carriers of virus. Although neutralization tests with these murine-adapted strains had been carried out on hospitalized patients in other epidemics, antibodies had not here-

tofore been looked for in paired serums of healthy carriers collected early and late in relation to the time of virus excretion

No significant change in antibodies to the murine-adapted strains as a result of exposure to the outbreak was demonstrable (Table 3). One of the carriers had no humoral antibodies and failed to develop any during the period of exposure. The serums of the other 2 carriers both contained antibodies at the time virus was first detected in the stools. There appeared to be a slight rise of questionable significance six weeks later.

Of the 3 healthy noncarriers of virus, 2 did not have humoral antibodies, nor did any develop during the interval of three to six weeks between collections. The third member of this group, on the other hand, maintained a constant antibody level during the six-week period.

### DISCUSSION

The attack rate in one group (the Blue Moccasin group) of Pfd campers was high. Of a total of about 31 campers, who were all, so far as is known, similarly exposed, 5 developed frank poliomyelitis, and of 18 healthy members of this group, 5 were found to be carriers. (The remaining 8 members were not available for study.) This gives a frank attack rate of about 5/31 (or 16 per cent) and an infection rate of 10/23 (or 43 per cent). This high incidence of disease was recognized only among the Blue Moccasin group, no cases occurred in the two other groups living under almost the same conditions.

Of the 5 carriers, 3 excreted the virus in the stools for at least three or four weeks. These findings are analogous to those encountered in similar studies on the frequency and duration of virus carriers among patients with clinical poliomyelitis. Further study is necessary to determine the possible epidemiologic significance of the prolonged period of excretion of the virus from the intestinal tract. Of the 5 carriers who returned to their homes, only 2 had siblings there. Throat swabs and stool samples were obtained from both these children, and all samples gave negative tests in monkeys. It was unfortunate that this part of the study was so limited as to render our few negative results of no statistical significance.

Similarly, the serologic studies were disappointing, for the homologous strain was not used. In other words, the Pfd strain was not found to be related to the Lansing and Y-SK strains. Had the serologic studies been performed with the Pfd camp strain, an entirely different result might have been obtained. This was not feasible because of the failure of this strain to be adapted to rodents.

### SUMMARY

An outbreak of infantile paralysis in a boy-scout camp attended by boys aged twelve to eighteen years is described. Although the camp was divided into three groups the occurrence of clinical cases was confined to only one of the groups, and the carrier-rate studies were similarly confined to this group.

Of the 31 members of this group, 5 developed frank poliomyelitis, with 4 bulbar cases, 1 of which terminated fatally.

Of the 18 healthy members studied in this group, 5 were revealed to be intestinal carriers of virus, and 1 of these also harbored virus in the throat.

Estimates of the total infection rate in this group were roughly 43 per cent, with a ratio of frank cases to carriers of about 1/2.

Of the 5 carriers, 3 excreted the virus in the stools for at least three or four weeks.

In the single carrier in whom the virus was isolated from both the oropharynx and the intestinal tract, virus was isolated from the stools for a period of about one month, it could not be found in the throat after the first week.

In 1 of the clinical cases, virus was isolated from both the oropharynx and the stools one day before the onset of symptoms.

Of 2 siblings exposed to virus carriers (1 of whom had virus in both the throat and stools), neither subsequently became virus carriers.

The strain of poliomyelitis virus isolated during the outbreak did not appear to be related to the Lansing and Y-SK strains by serologic test, nor could it be adapted to rodents even after many trials.

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## MEDICAL PROGRESS

## THE "NEPHROTIC SYNDROME"\*

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THE "nephrotic syndrome" is one of the most striking phenomena of renal disease. The combination of gross edema, hypoproteinemia, hypercholesterolemia, lipidemia and heavy proteinuria, in the absence of congestive heart failure, is unique and easily recognized. It frequently appears during the course of chronic diffuse glomerulonephritis (the nephrotic phase).<sup>1</sup> Other causes are renal amyloidosis, syphilis, intercapillary glomerulosclerosis and renal-vein thrombosis. In children and young adults the syndrome occasionally develops in the absence of renal disease as so-called "pure," "genuine" or lipid nephrosis. A prolonged debate has centered about this entity. It is claimed on the one hand that the disorder is renal in origin, either a disease entity *sui generis*<sup>2,3</sup> or the result of an unrecognized glomerulonephritis,<sup>4,5</sup> and, on the other, that it is primarily extrarenal, perhaps on the basis of some obscure derangement of protein metabolism.<sup>6,7</sup> Conflicting opinions regarding the pathogenesis of various manifestations are likewise unsettled, but there is general agreement that the "nephrotic syndrome" presents certain uniform and consistent features, whatever its etiology. The following discussion is devoted chiefly to a consideration of these aspects of the disorder.

## PROTEINURIA

One of the most impressive and characteristic manifestations of the nephrotic syndrome is the continuous loss of large amounts of protein in the urine. The resulting drain upon body protein and the stimulus to increased protein synthesis probably contribute in the pathogenesis of various associated phenomena, but unfortunately, too few unequivocal facts are available at present to permit an analysis of the situation as a whole. Indeed, the nature and source of urinary protein is still debated, and current concepts of the renal mechanism of protein excretion are speculative.

Analysis of proteins in blood and urine is handicapped by the lack of satisfactory methods for isolating pure components of the protein mixture. Fractional "salting-out" precipitation has been used for separating albumin from globulin. It is now known that these fractions are heterogeneous. The use of ultracentrifugation, electrophoresis and im-

munologic techniques indicates that at least five globulins and two albumins are distinguishable,<sup>8-12</sup> and it is believed by those intimately engaged in the work that even the refined fractions are not pure.<sup>14</sup> As Gutman<sup>15</sup> points out in an excellent review, the discovery that albumin obtained by fractional precipitation contains significant amounts of globulin is very important, since changes in the globulin content of the albumin fraction may account for apparent deviations from the normal.

The plasma protein composition is greatly altered in the nephrotic syndrome. All methods agree in revealing a marked reduction in albumin.<sup>16,17</sup> The globulin content may rise, especially in amyloidosis,<sup>18</sup> remain unchanged or fall.<sup>17,19</sup> Usually, the beta globulin and fibrinogen increase, the alpha globulin may rise when the albumin concentration is very low. Gamma globulin is almost always reduced.<sup>18</sup>

There is no reliable evidence that the plasma contains abnormal proteins. Plasma albumin, separated by precipitation, has a somewhat higher molecular weight and lower osmotic pressure than normal,<sup>19,20</sup> presumably because there is a larger proportion of contaminating globulin. Differences in fractions obtained by ultracentrifugation may also be explained on this basis.<sup>21</sup> Specific antisera to plasma albumin and globulin fail to precipitate nephrotic proteins quantitatively suggesting the presence of immunologically distinct proteins.<sup>8,22,23</sup> But it now appears that the unprecipitated portion of the albumin fraction is in reality globulin precipitated with the albumin during salting out. An abnormal distribution of globulins differing antigenically may be the cause of the anomalous behavior of nephrotic globulin.<sup>8</sup> Alving and Mirelsky<sup>24</sup> found that nephrotic plasma from which globulin had been removed by precipitation contains less cystine than normal. They attributed this to the appearance of a cystine-poor albumin, from which normal albumin could be removed by recrystallization. It has recently been shown,<sup>25</sup> however, that alpha globulin, the usual contaminant, contains very little cystine, and it now seems likely that the authors were dealing with this component and not with an abnormal protein.

Albumin preponderates in the urinary protein mixture. The electrophoretic pattern may resemble the pattern of normal plasma in showing a very large albumin peak even when plasma albumin is markedly depressed.<sup>19,26</sup> In some cases globulins may

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be prominent, apparently as a result of more extensive and severe renal damage.<sup>27</sup>

Evidence that abnormal proteins may appear in the urine has been vitiated by the failure to work with pure homogeneous fractions. It is interesting that the "abnormal" albumin detected in the urine by specific antisera, by high molecular weight and by low cystine content is always present in lower concentration than in the plasma.<sup>19, 21</sup> Proteins of small molecular size predominate in the urine,<sup>19</sup> and it is consistent with this tendency that the "abnormal" protein, probably globulin, should not readily enter the urine. The evidence indicates that proteins are excreted on the basis of molecular size, configuration and electrical charge, rather than on the basis of some intrinsic abnormality of composition, suggesting mechanical filtration from the plasma as the mode of excretion.

Certainly, there is much in favor of the belief that urinary proteins are derived from plasma. It has long been known that proteins in plasma and urine are coagulated and precipitated in the same manner.<sup>28</sup> More recently it has been found that precipitated protein fractions from the plasma and urine of a patient with nephrosis are identical so far as the optical rotation, specific refraction, racemization, osmotic pressure, nitrogen distribution and immunologic properties are concerned.<sup>22, 23, 29-32</sup> Even though these studies have not been made upon pure fractions they establish beyond reasonable doubt the source of urinary protein. Hence it may be concluded that urinary proteins are derived from plasma by a filtration mechanism.

The obvious site of protein filtration is the glomerulus, where continuous ultrafiltration of plasma water and solutes has been shown to occur normally.<sup>33, 34</sup> The presence of precipitated protein in the glomeruli of patients with proteinuria lends further credibility to this view. There is nothing to suggest that tubular protein excretion plays a role, but it is possible that altered reabsorption may be important.

Normally, protein does not appear in the urine in concentrations greater than 90 mg per 100 cc or in amounts exceeding 150 mg per day.<sup>35</sup> Thus, there is either insignificant passage of protein through the walls of the glomerular capillaries or almost complete removal of protein from the filtrate by tubular cellular activity. Samples of glomerular filtrate have been obtained in mammals by micropipette<sup>34</sup> and little or no protein detected, but the best methods available for the determination of proteins in such small volumes fail to show concentrations below 25 mg per 100 cc.<sup>36</sup> Hence, it is possible that the human glomerulus produces a filtrate containing 200 mg per 100 cc and that, assuming a normal daily filtration volume of 175 liters, 35 gm of protein may be made available in this way for possible loss in the urine. If these considerations are correct, a considerable proteinuria

might develop as a result of a failure of tubular protein reabsorption. Even then, however, insufficient protein would be excreted to account for the huge losses — as much as 60 gm per day<sup>37, 38</sup> — occasionally observed during the nephrotic syndrome. When it is remembered that, in addition, the plasma protein concentration is greatly reduced, with a lower filtrate concentration in consequence, and that the filtration rate may be less than normal, it becomes obvious that tubular dysfunction cannot be the sole basis for proteinuria. Increased filtration of protein must occur, apparently as a result of an alteration in the glomerular capillary walls rather than in the nature of plasma proteins. It is possible, of course, that reduced tubular reabsorption plays a contributory role, but the evidence presented below indicates enhanced rather than diminished protein reabsorption. Thus, regardless of etiology, proteinuria in the nephrotic syndrome is attributable to defective glomerular activity.

#### ALTERATIONS IN RENAL STRUCTURE AND FUNCTION

The renal structural alterations associated with the nephrotic syndrome are exceedingly diverse and often obscure. There is a paucity of pathological material owing to the fact that most patients recover from the disease or progress into some more advanced phase before death. Cases have been reported singly or in very small groups.<sup>39-43</sup> In such studies no characteristic lesion has been marked out, and in a certain proportion of cases no renal disease has been found. As a rule, however, glomerular and tubular lesions are present.

The glomerulus is the logical center of attraction, but the search for lesions is often disappointing. According to Bell<sup>6</sup> and others,<sup>44</sup> the basement membrane is the most important component of the glomerular capillary wall since the endothelium is delicate, sparse and possibly not intact. There is a small amount of connective tissue between capillary loops forming a mesentery-like supporting structure often referred to as the "mesangium."<sup>44, 45</sup> A thin epithelial membrane covers the entire filtering surface, reaching in between capillary loops and dipping down into the spaces between the lobules. Thickening of the basement membrane, proliferation of the intercapillary connective tissue and piling up of endothelial cells (though the last is denied by MacCallum<sup>46</sup>) occur characteristically in chronic diffuse glomerulonephritis. During the nephrotic phase these changes are not extensive. In only a few glomeruli has the process resulted in hyalinization and obliteration.<sup>5</sup> Thus, the total area of the filtration bed is not greatly altered, although it is evident that the changes in the nature of the filter might be expected to result in a somewhat different filtrate composition. Similarly, in other disorders giving rise to the nephrotic syndrome glomerular lesions that do not appear to encroach seriously upon the filtering area are found. In amyloid disease,

there is a deposition of complex protein, possibly related in some manner to antibody production,<sup>47</sup> in the pericapillary spaces between the basement membrane and endothelium.<sup>48</sup> With progression, of course, compression of capillaries and obstruction to blood flow may lead to glomerular destruction. The renal disorder associated primarily with prolonged diabetes mellitus, intercapillary glomerulosclerosis,<sup>49-52</sup> is characterized by the appearance of nodular masses believed to arise from sclerosis and hyalinization of intercapillary connective tissue. The capillaries are pushed apart, and the glomeruli may be strikingly deformed by this material. In contrast, the glomeruli in kidneys of patients, usually young children, dying during the course of lipid nephrosis present few or no alterations. There may be some increase in the nuclear content of a few glomeruli, and adhesions between the tuft and Bowman's capsule may be demonstrable in some areas.<sup>53, 54-56</sup> Bell<sup>5</sup> has reported diffuse thickening of the basement membranes in a few cases and claims to have found "pores" through which protein might escape into the urine. It is certain that there are no obvious glomerular lesions in many cases of the disorder. This is also true of the few cases of the nephrotic syndrome that have developed after thrombosis of the renal vein.<sup>57, 58</sup> The absence of glomerular lesions does not preclude capillary injury and increased protein filtration; however, since Walker and Oliver<sup>1</sup> found that protein appeared profusely in the filtrate after minor trauma to capillaries without visible injury.

The tubular pathology is almost always outstanding, after the disorder is well established.<sup>59</sup> Fatty and colloid substances appear as droplets or vacuoles in the tubule cells, particularly in the proximal segment. Nearly all the cells in this part of the nephron may be filled to bursting with brightly refractile fat.<sup>67</sup> The deposit is distributed irregularly, and groups of grossly swollen cells bulging out through the basement membrane may give rise to contortion and kinking of the tubules. In many places the nuclei are pyknotic, and there may be necrosis with desquamation of portions of the tubular epithelium. As a result of these changes, which occur in every type of the nephrotic syndrome, the kidneys become large, pale and rather yellowish and firm but not fibrotic. A few microscopic scars may be found scattered through the parenchyma, to a greater extent perhaps in the nephritic and amyloid forms, but rarely sufficient to cause grossly detectable fibrosis or contraction.

The source of the cellular inclusions typical of the nephrotic kidney is not settled. They were at first considered a result of cellular degeneration. The demonstration that the lipid content of the kidneys is increased<sup>68</sup> appears to indicate, however, that intracellular fat is not unmasked by a change in physical state (fat phanerosis) but is deposited from without. The nature of the hyaline colloidal mate-

rial has been elucidated by Gérard and Cordier,<sup>69</sup> Smetana and Johnson<sup>70</sup> and others who have approached the problem through comparative physiology. In the salamander a certain number of nephrons communicate directly with the peritoneal cavity, whereas others do not ("open" as opposed to "closed" nephrons). After intraperitoneal injection of solutions of various proteins bound to dyes and of nephrotic serums, brightly stained droplets of protein and doubly refractile bodies are found only in cells throughout the length of the open nephrons, none appear in cells of the closed nephrons. These findings support the conclusion that the reabsorption of protein and lipids from the glomerular filtrate by the tubules might account for the tubular pathology of the nephrotic syndrome. A similar phenomenon has been observed in mammals.<sup>71, 72</sup> Administration of protein-dye compounds to rats with proteinuria results in the appearance of deeply stained globules in the cells of the proximal segment. In the absence of proteinuria these substances do not pass into the urine, and tubular lesions do not develop.

Such data must be used cautiously in the interpretation of the tubular changes in nephrosis in man. There are excellent reasons for the belief that there is protein filtration, and it certainly seems probable that reabsorption of protein from the filtrate may induce certain alterations in cell structure. It is unknown, however, whether these changes are based upon overactivity of normally active reabsorptive mechanisms. Oliver<sup>73</sup> objects to the notion that the large, obviously destructive deposits of fat result from such overactivity because the deposits are irregularly dispersed. There is no information available regarding the distribution of reabsorbed protein in the tubular cells or its relation to fat infiltration. Fat tends to accumulate in injured cells,<sup>74</sup> and it is possible that a similar process occurs in the kidney after injury by excessive protein reabsorption. In the nephrotic syndrome the blood contains a high concentration of lipids in the colloidal state apparently forming large complexes with various globulins.<sup>75</sup> It is probable that such compounds are not readily filtered even when albumin traverses the glomerular membrane with ease. In line with this view is the low concentration of lipids in the urine, despite marked lipidemia.<sup>76-78</sup> That which appears in the urine seems chiefly to be contained within the desquamated tubular cells comprising the numerous urinary casts. Centrifugation of the urine removes most of the detectable lipids, apparently by removing this cellular debris. Hence it is not unlikely that fats and cholesterol enter the tubule cells from the blood rather than from the glomerular filtrate. Further study is necessary to answer this question.

The urine is often highly concentrated, containing cellular elements or casts of various kinds in great numbers. Erythrocytes, leukocytes and epithelial

cells may appear abundantly in the urine. Hematuria has been considered exceptional, but repeated examinations of the urine disclose showers of red cells from time to time in nearly every patient. Even in lipoid nephrosis, in which the absence of blood from the urine is regarded as a *sine qua non*, red cells are occasionally found. Casts are composed of coagulated protein, alone, or binding a heterogeneous mixture of cells and cellular material. In view of the high concentration of protein in nephrotic urine it is rather surprising that cast formation is not more impressive than it is. High concentrations of salts and urea have a dispersive influence upon proteins in solution, whereas reduction of the reaction of the glomerular filtrate during its passage down the tubule tends to favor precipitation.<sup>57</sup> There is some evidence that the introduction of a protein precipitant by tubule cells is necessary to disrupt these balancing influences, and to bring about protein coagulation.<sup>57</sup> Whether cast formation is restrained in the nephrotic syndrome by adequate concentrations of various dispersive solutes or by insufficient precipitant is unknown.

On the whole, kidney function appears to be excellent. Many writers have stressed the normality of concentrating power, phenolsulfonephthalein excretion and urea clearance and the absence of nitrogen retention, acidosis and other evidences of renal insufficiency.<sup>2, 55, 56</sup> Considering the state of the kidney it is not surprising that this should be so. Although glomerular lesions are demonstrable, there is little or no destruction of glomeruli. Hence filtration should not be greatly affected. The renal vascular system is relatively undisturbed, and blood continues to perfuse renal tissue normally. Although the tubular lesions may be striking, little loss of nephrons is incurred. Renal functional alterations are demonstrable only by more refined techniques in most cases, particularly in lipoid nephrosis. Occasionally, however, the disturbance is more profound. Indeed, evidence of renal insufficiency develops sooner or later in most cases of the nephrotic syndrome in which progressive renal damage occurs, as in the course of chronic diffuse glomerulonephritis, intercapillary glomerulosclerosis and amyloidosis.

The glomerular filtration rate is usually reduced moderately, to values as low as 50 per cent of normal in many patients with chronic renal disease.<sup>67-69</sup> In children with lipoid nephrosis, on the other hand, the filtration rate may be increased markedly.<sup>70-72</sup> The urea clearance tends to follow filtration rate and to present similar decrements and increments. Although the possible causes of diminished filtration are obvious, it is difficult to explain the augmentation in children. Such a change may be the result of increased effective filtration pressure secondary to a vasomotor adjustment or to the fall in plasma oncotic pressure due to hypoproteinemia.

In the few cases studied thus far renal blood flow has been found within normal limits or slightly decreased.<sup>67-69</sup> In lipoid nephrosis elevations in blood flow have been reported.<sup>72, 73</sup> What these changes may imply regarding vasomotor activity within the kidney we cannot at present state with any certainty.

Tubular function is usually unaffected. Various measurements, such as those by glucose, Diodrast and para-aminohippurate Tm, tend to be normal despite the reduction in filtration.<sup>69</sup> Thus, the stream of urine may flow more slowly down the tubule, prolonging its contact with active reabsorptive cells and providing an improved opportunity for reabsorption of water and solutes. This phenomenon of glomerulotubular imbalance may account for continued normality of concentrating power and for occasional fixation of urinary specific gravity at a high level. It is possible, too, that urea reabsorption may be enhanced in this manner to give rise to the modest elevation in blood urea sometimes observed. Certainly, the tubule cells appear to acquit themselves well. Not only can they reabsorb water and electrolytes normally or even in excess but also they are capable of adequate excretion of hydrogen ion and of ammonia synthesis.

Renal functional and anatomic abnormalities are thus demonstrable in every case of the nephrotic syndrome. They vary considerably in kind and degree, but are never so severe as to suggest extensive damage and loss of tissue. These processes are characteristically reversible. Every trace of the disorder may disappear, and the kidneys return to normal in many patients, even after a prolonged illness. In others, however, parenchymal damage may finally ensue with the development of renal insufficiency as nephrons disappear and the glomerular filtration bed shrinks. In this process the nephrotic syndrome clears.<sup>55, 56</sup> Proteinuria is less marked and may ultimately cease altogether, apparently as a result of the obliteration of defective glomeruli and the diminution in the available filtration surface through which protein may escape from the blood. As protein loss diminishes, the plasma protein concentration rises and peripheral edema regresses.

### (To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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#### CASE 34071

##### PRESENTATION OF CASE

A fifty-seven-year-old man entered the hospital because of a lump in the right upper quadrant.

The patient's attention was first called to his abdomen three weeks prior to admission when he had an acute pain in the region of the umbilicus while attempting to lift a plank. The pain persisted for two hours and then disappeared completely; it was not accompanied by nausea, vomiting or other gastrointestinal symptoms. At that time he noted the mass, which was tender and which in the following three weeks grew slightly larger and moved up and to the right. Following the discovery of the mass he limited his food intake, and his bowel movements became somewhat more scanty, having previously been regular. The only change noted in the character of the stools was that they were perhaps somewhat lighter in color. An estimated 10 to 15 pounds of weight had been lost during the present illness.

The patient had been addicted to morphine for thirty-seven years, a habit initiated by taking the drug for several attacks of right-lower-quadrant pain diagnosed at the time as chronic appendicitis. Six major and numerous minor attempts were unsuccessful in breaking the habit.

Physical examination showed a slender, rather nervous man. There were numerous injection scars on the arms and thighs. Examination of the heart and lungs revealed only emphysema. The abdomen was flat and soft throughout. In the right upper quadrant there was an irregular, firm, movable, tender mass, 8 by 6 cm. in diameter, which appeared to be attached posteriorly but was thought not to be connected to the liver.

The temperature, pulse and respirations were normal. The blood pressure was 160 systolic, 85 diastolic.

Examination of the blood showed a hemoglobin of 13.5 gm. and a white-cell count of 10,400. The urine was normal. Two stool specimens were guaiac

negative. The nonprotein nitrogen was 31 mg. per 100 cc., the total protein 8.18 gm., with 4.53 gm. of albumin and 3.65 gm. of globulin, the phosphorus 3.5 mg. and the phosphatase 4.9 units. The van den Bergh reaction was normal, and the cephalin flocculation test +++ in twenty-four and forty-eight hours.

An x-ray film of the chest disclosed findings consistent with emphysema, a barium enema showed no evidence of disease intrinsic to the large bowel and no evidence of external compression, an intravenous pyelogram demonstrated no evidence of disease of the urinary tract, a gastrointestinal series was not completely satisfactory but no abnormalities were made out, and a cholecystogram showed no definite evidence of a gall-bladder shadow. On one film the right kidney and its pedicle were seen to be outlined more clearly than usual.

On the tenth hospital day an operation was performed.

##### DIFFERENTIAL DIAGNOSIS

DR. RICHARD H. SWEET: As we progress with this history the real decision that we have to make is whether the tumor, which was very obvious in the patient's abdomen, had anything to do with the trauma that is described, because the record mentions that the patient's attention was first called to the abdomen when he had acute pain in the region of the umbilicus while attempting to lift a plank. It is a very short history. I do not know whether he was a good plank lifter or not, but people accustomed to lifting heavy weight know how to do it, so that they do not rupture a deep epigastric artery and cause abdominal-wall tumors of traumatic origin. I am rather inclined to discount the trauma. At any rate he felt the pain and this pain was short-lived — lasting only two hours in duration and disappearing completely — and we assume that it never came back.

"Following the discovery of the mass he limited his food intake." That statement makes no sense, since it does not reveal why he limited the food intake. He had no nausea or vomiting, and was supposed to feel well. Limitation of food intake is unusual simply because a patient feels something in the abdomen. Perhaps his doctor had something to do with it.

The fact that the patient was a morphine addict is important, because I believe that it makes the history completely unreliable. I have never seen a morphine addict who could tell a straight story about anything, especially about his own symptoms. That discourages me. I do not consider this history worth anything in the making of a correct diagnosis.

I should say that the laboratory findings were within the normal range. I imagine that liver disease was looked for, and I assume that there was no evidence of it.

I also assume that the gastrointestinal series was not repeated even though it was not satisfactory. I suppose that the cholecystogram revealed a shadow, but the examiners were not sure of it, it was not definite. That is the only thing about the x-ray examination that interests me.

On one film the right kidney and its pedicle were seen to be outlined more clearly than usual. I do not understand what that means. Did the patient have some retroperitoneal gas or some air outlining the kidney and its pedicle? That is unusual to see, is it not, Dr. Wyman?

DR. STANLEY M. WYMAN: Yes. The chest is clear but shows emphysema. The patient did have two gastrointestinal examinations. They show a normal-appearing stomach and duodenal bulb and loop. There is a little calcification in the left upper quadrant, which probably lies in the splenic vessels. On one of these films that cannot be seen clearly, there is a somewhat irregular pattern of the esophagus, which makes me raise the question of possible varices. I cannot make a definite statement because the film is not sufficiently good.

DR. SWEET: You do not see any definite mass?

DR. WYMAN: The right colon is pushed down somewhat. That may be a large liver, or possibly a mass that cannot be outlined.

DR. SWEET: I think it is stated somewhere that the mass was attached posteriorly and that it was not connected to the liver. That is an important observation, if we are going to decide what this mass might be. The statement may be correct, it may not be. I know that I can make that error myself. I have occasionally seen an enormous hydrops of the gall bladder in which the fundus of the gall bladder felt very much like an ovarian cyst lying in the right lower quadrant of the abdomen. The problem resolves itself into a very simple matter of deciding what the abdominal tumor was. Presumably it was of short duration and was easily felt by the physicians in attendance. It was a hard, irregular, movable mass not connected with the liver but attached posteriorly. The gall bladder is usually smooth and not irregular, unless it is involved in carcinoma. It is almost always attached to the liver. A carcinoma of the duodenum is excluded by the x-ray findings, as is carcinoma of the pancreas. A renal-cell carcinoma would also have shown some abnormality of the kidney shadow in the intravenous pyelogram. Carcinoma or other tumor of the hepatic flexure ought to be thought of, but there again the x-ray film ought to exclude it. That brings us down to the assumption that this tumor was retroperitoneal, one of those unusual mesenteric cysts, or something of that sort. But it was hard and irregular, so that we might on that basis exclude such a diagnosis. I should like to mention lymphoma, but the retroperitoneal lymphomas that we see are usually farther over to the

midline, almost always fairly fixed in the posterior aspect of the abdomen.

I should like to return again to the question of trauma, because I should at least mention the possibility that there was a hematoma from a ruptured vessel from lifting the plank. Trauma of that sort is most apt to cause rupture of the deep epigastric artery, and then of course the tumor lies in the rectus sheath. In that case the patient has cramping pain, which does not disappear in two hours. It brings the patient into the hospital. An emergency operation is often performed because the pain is so intense, although the diagnosis can be made ahead of time.

Having mentioned most of the possibilities that I can think of, I am inclined to agree that this was a surgical case and that the patient should have been operated on, but I think it is very premature to attempt to make a diagnosis.

DR. BENJAMIN CASTLEMAN: Does anyone wish to offer to make a more definite diagnosis?

DR. WYMAN: I wonder if Dr. Sweet would consider the possibility of hepatoma very early.

DR. SWEET: Yes, I intended to speak of it. Tumor of the liver, although the mass is not connected with the liver on physical examination, should be mentioned — a tumor arising in the liver on a pedicle. I have actually seen such a tumor.

DR. WYMAN: My reason for mentioning it is that if the esophageal irregularity pointed to varices, that diagnosis might occur.

DR. SWEET: I excluded that possibility because the gastrointestinal tract was normal.

#### CLINICAL DIAGNOSIS

Carcinoma of gall bladder?  
Carcinoma of bile ducts?

DR. SWEET'S REPLY

Morphinism

#### ANATOMICAL REPLY

Subacute and chronic perforation  
Cholelithiasis

#### PATHOLOGICAL REPLY

DR. THOMAS GREEN: To reconfirm course, by the history I have the ad of peritoneoscopy body, which is included in the report of the Benedict as shown in the retroperitoneal area, I am sure I might say that the

ward this mass was well below the liver edge and did not seem to move with the liver, although he did not have, as I remember it, marked excursion of the liver on inspiration and expiration

At operation we explored the right upper quadrant, and on opening the abdomen we found a large mass covered with omentum extending down the right side of the abdomen. It was found to be attached to the transverse colon, and when it was freed, it became obvious that it was an acutely and chronically inflamed gall bladder, the thickened wall extending to the level of the umbilicus. When we first felt it, it was so hard that we thought that it was carcinoma. On freeing it from the omentum, we broke into it, and a large amount of yellow pus escaped. It was necessary to free it from the transverse colon with sharp dissection, and we found numerous stones, one of which — a large one — was impacted in the ampulla of the gall bladder at the beginning of the cystic duct. In retrospect, putting the picture together, we thought that the patient had an inflamed gall bladder completely masked by the morphine addiction, probably, as he lifted the plank the gall bladder ruptured and he developed a localized peritonitis, which fortunately for him he was able to tolerate well. The wall of the gall bladder in one place was 2 cm thick. After we removed it we asked the laboratory to do a frozen section, and there was no evidence of carcinoma.

DR CASTLEMAN There was a piece of tissue removed from outside the gall bladder that showed a gallstone surrounded by foreign-body reaction, so that we have proof that the gall bladder had perforated, probably after the patient lifted the plank three weeks previously. The wall showed a subacute and chronic inflammatory reaction but no carcinoma.

## CASE 34072

### PRESENTATION OF CASE

A forty-one-year-old gasoline-station operator entered the hospital complaining of boring epigastric pain.

Five years prior to admission the patient first experienced pain in the epigastrium, occurring after meals and relieved by food or alkali. A Graham test two years before admission failed to visualize the gall bladder. Following this, an operation was done, and the gall bladder was not found. An appendectomy was performed. The pain reappeared after a year's alleviation following operation. He had been eating "anything and everything."

Physical examination of the chest and abdomen was negative, there was a healed scar over the right rectus muscle.

The blood pressure was 130 systolic, 85 diastolic

Examination of the blood disclosed a hemoglobin of 15.3 gm and a white-cell count of 10,900. Urinalysis gave a specific gravity of 1.012, and was negative for sugar, albumin and diacetic acid, rare white cells and epithelial cells were seen in the urinary sediment. A gastrointestinal series showed enlargement of the gastric rugal folds. The duodenal bulb was constantly deformed and showed pooling of barium in the midportion, with a surrounding area of rarefaction, consistent with edema about a crater.

On the fifth hospital day a subtotal gastrectomy, with a gastrojejunostomy, was done. Two days later the patient's condition was "alarming," with low blood pressure, a thin rapid pulse, peripheral vascular collapse and cyanosis. The temperature was 102°F orally. The chest was clear. The abdomen was silent and only slightly distended. Penicillin and streptomycin were started. Following this, he passed very little urine, and the nonprotein nitrogen rose to 110 mg per 100 cc on the third postoperative day. Because of tenderness and spasticity in the right upper quadrant an incision was made and about 1000 cc of "grossly uninfected bile" was drained. On the fifth day, following the original operation, the temperature remained elevated, and the nonprotein nitrogen rose to 165 mg per 100 cc. The serum amylase was reported as 100 units, and atelectatic areas were visualized at the right base by x-ray examination. The patient expired on the eighth day following the original operation.

The fluid exchange during and after the operation was as follows:

	INTAKE		OUTPUT	
	INTRAVENOUS cc	ORAL cc	URINE cc	LEVINE TUBE cc
Day of operation				
Transfusion	1000			
5 per cent dextrose in water	1500			
5 per cent dextrose in physiologic saline solution	1000	0	Unknown	0
First day				
5 per cent dextrose in water	1200			
10 per cent Amigen	1000	360	120	1000
Second day				
Transfusion	500			
10 per cent Amigen	1000			30
Third day				
Transfusion	500			
5 per cent dextrose in physiologic saline solution	300			
5 per cent dextrose in water	1300		120	750
Fourth day				
Transfusion	500			
5 per cent dextrose in physiologic saline solution	500			
5 per cent dextrose in water	2200			720+
10 per cent Amigen	1000			2000*
Physiologic saline solution	100		470	
Fifth day				
5 per cent dextrose in physiologic saline solution	1600			
5 per cent dextrose in water	1500		850	750
Amigen	900			

\*Estimated amount lost at time of incision and drainage.

	INTAKE		OUTPUT	
	INTRAVENOUS	ORAL	URINE	STOMACH TUBE
Sixth day:				
5 per cent dextrose in physiologic saline solution	1700			
5 per cent dextrose in water	400			
5 per cent Amigen	1000		1250	240
Seventh day:				
5 per cent dextrose in physiologic saline solution	2500			
5 per cent dextrose in water	500		1630	Unknown
Eighth day:				
5 per cent dextrose in physiologic saline solution	500			
5 per cent dextrose in water	2700	1150	1580	690

## DIFFERENTIAL DIAGNOSIS

DR. CHARLES L. SHORT: May we see the x-ray films?

DR. STANLEY M. WYMAN: There is a small hiatal hernia seen on all films. There is slight prominence of the gastric rugae. The duodenal cap is strikingly deformed, constantly throughout two examinations. The small pool of barium seen proximally in the cap may represent a crater or possibly barium caught between folds. The duodenal loop is normal in size and contour. There is no evidence of excretion of the gall-bladder dye on one examination. The post-operative film of the chest taken with a portable apparatus shows atelectasis at both bases, but clear lung fields otherwise.

DR. SHORT: Would you say that a definite ulcer crater was demonstrated?

DR. WYMAN: In going back over the films, I am not entirely convinced that it is. I think that it might perhaps more readily be interpreted as barium between folds for the reason that the contour appears to change and a crater would remain constant.

DR. SHORT: Do you see any air or barium in the hilum?

DR. WYMAN: No, I do not.

DR. SHORT: Do you think that these defects could be caused by adhesions outside the duodenum, such as pericholecystitis?

DR. WYMAN: They are more consistent with a deformed cap from an old duodenal ulcer.

DR. SHORT: We have a reasonably certain x-ray diagnosis, then, of an active duodenal ulcer, although the roentgenologist is not quite willing to say that the picture is absolutely diagnostic. The patient's history seems typical of this condition, including a year of remission of symptoms. Perhaps a different history given two years before directed attention toward the gall bladder, and at that time a positive Grabam test was obtained.

The next statement is a surprising one — that the gall bladder was not found at operation. I can think of three possible explanations for this, although there may be more. The patient may have had congenital absence of the gall bladder. This is a rare condition, but cases have been recorded.

The second is that the gall bladder occupied an anomalous position, perhaps embedded deep in the liver, or was covered by a congenital band. The most likely possibility, I think, is that identification of the gall bladder was difficult on account of adhesions in that neighborhood. In view of the x-ray findings the source of the adhesions may well have been a healed perforation of a duodenal ulcer, although we must still bear in mind the possibility that the patient had cholecystitis. Physical examination is not helpful, and the urinalysis gives no hint of underlying renal disease. We can assume that the preoperative diagnosis was duodenal ulcer and that the indications for operation were that the patient was unable or unlikely to follow a medical regime. Since a gastric resection was performed, fairly good evidence of duodenal ulcer must have been found at operation. I shall be interested in hearing later more details of the findings, especially regarding the presence or absence of the gall bladder and of adhesions in that area.

Two days after operation the patient's condition suddenly became worse, with the development of fever and a state of shock. Examination of the abdomen revealed the development of at least a localized peritonitis. In view of the drainage of large amounts of bile two days later, it seems to me that the conclusion is inevitable that the patient had peritonitis that had arisen at the duodenal stump, either from leakage or from actual rupture. A more remote possibility is that the patient actually had gallstones and that one had ruptured through the gall bladder or common duct with the development of bile peritonitis. Acute pancreatitis is another possibility. Certainly it would be a rare complication of an operation in this area. I do not see how one could make that diagnosis from the evidence at hand. I do not believe that the elevated serum amylase is significant in view of the degree of renal failure. If we accept any of the diagnoses I have mentioned, the absence of pain at the time of this catastrophe would be unusual. In view of the history and x-ray films and the findings at operation, I shall assume that the patient did not have cholecystitis and am willing to eliminate that diagnosis.

We can only speculate regarding the cause of the duodenal leakage. From the figures that we are given on fluid exchange I do not believe that we can say that the patient was given too much water and salt immediately after operation, with the consequent development of edema and obstruction in the region of the stoma. Following the development of peritonitis the patient's course was marked by anuria succeeded by oliguria and the gradual resumption of a respectable urinary output. Except for the fourth postoperative day, when drainage was done, he maintained a positive fluid balance. The nonprotein nitrogen rose rapidly, however,



reaching 165 mg per 100 cc by the fifth post-operative day. The amount of fluid lost through external drainage is not recorded after the first day, and he undoubtedly continued to lose large amounts of fluid, electrolytes and protein through exudation into the peritoneal cavity. It is possible that the azotemia was due to the extrarenal causes I have mentioned, but more likely to some form of severe renal damage. I am referring to lower-nephron nephrosis, the common etiologic factors of which are shock, intravascular hemolysis and sulfonamide toxicity. He certainly went through a period of shock, intravascular hemolysis is possible since he received 1000 cc of blood, but we have no record of sulfonamide administration. Further data on the blood chemistry would be of interest but not diagnostic. The urinary findings, especially his ability to concentrate, would also be helpful. He evidently did not develop obvious edema, and we have no record of a blood-pressure rise before death.

It is hard to decide whether he died from sepsis or renal failure—probably a combination of the two. It is possible that he might have pulled through in the absence of peritonitis since he had an adequate urinary output in the last three days. It is difficult from the data at hand and without seeing the patient to comment on the fluid therapy that was employed. The amount of salt and fluid given the patient following the development of anuria seems contrary to the accepted principles of tiding over a patient with lower-nephron nephrosis with minimal amounts of both until renal function is resumed. But this patient in view of losses through drainage and exudation seemed to need more fluid and salt than the 500 to 1000 cc, including 300 cc of physiologic saline solution, which is usually prescribed by those who have studied this type of renal damage. However, I think that therapy may have been a little too enthusiastic and that some edema of the lung and other tissues was found at autopsy. In conclusion, I shall offer the following diagnoses: duodenal ulcer, bile peritonitis secondary to leakage from the duodenal stump and lower-nephron nephrosis.

DR TRACY B MALLORY: Dr Welch, will you discuss the operative findings?

DR CLAUDE E WELCH: The treatment that the patient had before he came to the hospital represented a long series of medical attempts with alkalies and bland diet, with never any relief of

symptoms, so that he was very unhappy about the situation and something was needed surgically. We believed that there was a certain amount of difficulty in making a clear-cut diagnosis, especially in view of the previous surgical findings. Therefore, I decided to do a laparotomy with a gastric resection, if he turned out to have an ulcer, rather than a transthoracic vagotomy. He turned out to have a large duodenal ulcer, one that was nonresectable. In other words, it involved the whole first and second portions of the duodenum, running down to the common duct. Consequently, I elected to do a procedure that was originally described by Finsterer<sup>1</sup> and later by Wilmanns<sup>2</sup> and others, in which the stomach is transected proximal to the pylorus, the entire mucous membrane of the pyloric segment removed and the muscularis of the stomach closed. One of the difficulties of this type of operation is the danger of leakage from the gastric stump, which does not heal so well as the duodenum. To date we have had no fatality from this course, and the operation has been carried out in 30 or 40 cases. The blood supply seemed to be extraordinarily good at the time, and we were successful in getting an excellent closure.

The postoperative course was of interest, and Dr Short has analyzed it very accurately. A great deal of blood chemical study was done but not recorded in the printed summary. It became obvious at the end of sixty hours that the patient was not doing well. There was a lengthy discussion regarding whether to do an exploratory incision at that time to discover the cause of the trouble. An exploration was carried out, and bile peritonitis, presumably from a leak of the gastric stump, was found. Thereafter fluids were given in accordance with the blood chemical findings. The chloride was almost constantly low, which explains the fact that he received a rather high intake of chlorides.

DR BENJAMIN CASTLEMAN: What about the gall bladder?

DR WELCH: I could not find it at the time of operation.

DR SHORT: If the diagnosis of lower-nephron nephrosis is correct, the low chloride might have been explained on the basis of increased plasma volume.

DR WELCH: A tremendous amount of chloride was being lost through the abdominal drainage, it could not be accurately estimated.

DR JACOB LERMAN A certain amount of Amigen sometimes elevates the nitrogen faster than it can be excreted in the urine. It may be just a temporary situation.

DR MALLORY The patient had a definite oliguria that lasted four days, an output below 500 cc. on each of these days, and this figure is the minimum output that will clear nitrogenous waste products.

#### CLINICAL DIAGNOSES

Bile peritonitis  
(Duodenal ulcer)

#### DR. SHORT'S DIAGNOSES

Duodenal ulcer  
Bile peritonitis, secondary to leakage from duodenal stump  
Lower-nephron nephrosis

#### ANATOMICAL DIAGNOSES

Duodenal ulcer, chronic  
Operative wound, gastric resection and gastroenterostomy  
Perforation of pyloric stump  
Peritonitis, generalized, acute, with fat necrosis  
Lower-nephron nephrosis, healing  
Congenital anomaly — absence of gall bladder

#### PATHOLOGICAL DISCUSSION

DR. MALLORY Autopsy showed, as was expected, a perforation of the stump of the gastrectomy. There was an old scarred duodenal ulcer. There was no gall bladder. There was a slight diffuse peritonitis accompanied by many foci of fat necrosis throughout the peritoneal cavity, indicating that duodenal contents had made their way around through the gastroenterostomy and the perforation in the pyloric stump.

The kidneys were significantly enlarged, the combined weight being 450 gm. Microscopically they were interesting to me because they showed a subsiding but definite lower-nephron nephrosis as Dr. Short predicted. In these cases the tubules are usually rather massively blocked with hemoglobinuric casts. In this case only traces were left. On the other hand there were well marked degenerative changes in the epithelial cells of the lower segments of the nephron. There was the usual interstitial inflammation between the straight tubules, most marked at the junction of the cortex and medulla, and there were some of the interstitial granulomas that are frequently seen from the fourth to the fifth day in lower-nephron nephrosis. There was also a definite degree of cloudy swelling in the proximal tubules, which I think is not a characteristic part of the picture although there is some difference of opinion about that. So far as the kidneys were concerned, I believe that the patient could have survived. He had gone through the acute stage and had re-established fairly adequate urinary output, and the histologic picture in the kidney corresponds with that very closely. This was evidently a healing lesion.

DR. SHORT Were the lungs edematous?

DR. MALLORY There was only slight pulmonary edema. There was nearly 2 liters of fluid in the abdomen.

A PHYSICIAN Did the fluid contain much bile?

DR. MALLORY At the time of autopsy it was not so darkly bile stained as the fluid previously drained.

DR. SHORT From the autopsy findings parenteral fluid and salt were certainly not given in excess.

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## BLUE CROSS

MUCH has been said and a great deal has been written during the past year about Blue Cross plans and their difficulties. In view of certain doubts and confusions that have arisen, it seems not only opportune but also most fitting that a careful analysis be made of a service that now makes available hospital care for almost thirty million of the American population.

It is essential to have in mind the purpose of the founding fathers of Blue Cross. This may be summarized as an effort to provide financial protection against the hazards of unpredictable illness, and the plans have been exceedingly helpful to their subscribers in making this protection possible through the years of Blue Cross existence. Until caught in the spiral of inflation, the plans have been helpful

to hospitals by guaranteeing reimbursement, with the advantage of an assured source of income, which has made budgetary planning, in a degree, easier and more secure. The importance of this factor can be better appreciated when one realizes that from 40 to 60 per cent of persons hospitalized in Massachusetts are Blue Cross subscribers. In view of this fact, Blue Cross must justifiably be considered a valuable voluntary instrument for protection against all, or part, of the hospital bill.

Varying methods of reimbursement to hospitals are in vogue throughout the country. Some are on the basis of established hospital charges, some on costs, and others in accordance with a previously agreed rate. Last June there was adopted in Massachusetts what is termed an all-inclusive plan—namely the furnishing to the subscriber of almost his total hospital needs. In the face of the continuing increases in the cost of hospital operation, this change played its part in the development of the present unsatisfactory situation. This is explained by the fact that whereas the costs were increasing, both subscription rates to subscribers and reimbursements to hospitals were expected to remain fixed for a period of a year. Factors of influence in Massachusetts that add to Blue Cross financial difficulties are a high incidence of admissions and a longer average hospital stay than occurs under other Blue Cross plans, with a consequent serious drain on Blue Cross financial resources.

The public, the hospitals and the medical profession must all play their part in the preservation of Blue Cross. To do this calls for cold, keen and careful analysis. The fear of increasing Blue Cross subscription rates must not be exaggerated or over-emphasized, for the American public is conscious of increasing costs in every line of endeavor and has shown its willingness to pay for what it receives. The zeal for maximum enrollment of subscribers on the part of those charged with this responsibility must not overshadow actuarial safety and sound financial management. Through it all, thinking and planning must be along a specific line—namely, the best interests of the public, which, after all, pays the bills. In exercising this concern and interest, the solvency of both the hospital and Blue Cross must be protected.

It is not too much to ask on behalf of the hospitals that Blue Cross subscribers do not add materially to their financial burdens. In the interests of mutual interdependence, it must be remembered that it is vital to the success of Blue Cross plans that hospitals remain financially sound, and it is not wise, when plans for the provision of voluntary care are extended, that either Blue Cross or hospitals should sustain financial losses. In the long run this must spell insolvency for one or the other, or both. If Blue Cross is to sell good hospital care, hospitals must be adequately compensated for furnishing that care. We cannot, therefore, escape the basic principle that the consumer, for whom the plan is provided, must pay an adequate premium or assume some portion of the risk that makes possible the service that he receives.

In conclusion, although it must be confessed that all is not well, it must also be realized that the patient (in this instance, Blue Cross) is not beyond cure and will be restored to health and usefulness if the public, the Blue Cross itself, the hospitals and the medical profession all do their part. If Blue Cross is to continue, as it should and *must*, the hospitals must support it staunchly, and those responsible for Blue Cross policy and management must be ever mindful that hospitals cannot endure without adequate reimbursement for the services that they render.

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## HELP FOR THE EPILEPTIC PATIENT

ELSEWHERE in this issue of the *Journal* a survey by the American Epilepsy League entitled "Who Cares for the Epileptic?" deals with the persons with seizures (more than 90 per cent) who are treated — if treated at all — by physicians in private office or in clinic. The survey does not deal with two other important aspects of epilepsy: the care of the minority group in tax-supported hospitals, and the interest of the general public in this segment of the sick population.

The year 1948 marks the semicentennial of the opening of the Monson State Hospital for epileptic patients, near Palmer, Massachusetts. Dr. William N. Bullard, backed by the Massachusetts Medical Society, provided the impetus for this project. The

third colony in the United States specifically for the care of epileptic patients, Monson is probably second to none in the effective use of available resources. However, the facilities both in capacity and in personnel are sadly inadequate to meet the demand. Physicians, parents of patients or patients themselves look despairingly at the long line of applicants waiting for months or years before doors that seldom open. Neither the parents manacled to a defective, seizure-ridden and perhaps unmanageable child nor the adult patients who are sound of muscle and mind but cannot keep a job because of uncontrolled convulsions are in a position to complain of the sort of physical and medical care that costs a total of less than \$1.50 a day, including less than 40 cents a day for food. (In sharp contrast, the amount paid by taxpayers for the hospitalization of epileptic veterans is approximately ten times greater.)

The obvious solution to the plight of the hundreds of waiting patients is more beds (in which there has been no increase at Monson for more than twenty years) with, of course, a larger budget both to maintain the beds and to provide wages high enough to attract personnel. However, the present yearly cost of institutionalized epileptic patients in Massachusetts is already in excess of a million dollars, and dispensers of public funds will want to know the causes for the present congestion and whether other alleviating measures might also be instituted.

The subject merits a broad and disinterested study, but two causes of congestion are immediately apparent. With bed space static, new patients cannot enter unless old ones leave. Thanks very largely to the development of the electroencephalograph and of more effective drugs in the last two decades, the control of seizures has been vastly improved. An increased turnover of institutionalized patients might be anticipated, but the present combined death and discharge rate of approximately 10 per cent is less than half the rate that obtained in the bromide period thirty years ago. Instead of developing a more rapidly moving stream of patients entering and leaving, epileptic colonies are becoming stagnant pools. Advanced medical care given to the hopelessly defective and a lack of social science

for the hopeful patients tend to block the exits of the institution. The lives of imbecile children with brains undeveloped or irreparably damaged, whose only hope is death, are prolonged through the conscientious use of prophylactic inoculations against childhood infections. Thanks to the sulfonamides and penicillin, pneumonia is no longer the friend of the aged to the extent that it once was. Tuberculosis, formerly a 10 or 12 per cent contributor to death in institutions, is under control at Monson. A recent survey by means of chest films disclosed less tuberculosis than in the outside population.

However, the decrease in exits because of death has been less in recent decades than the decline in the discharge of living (usually improved) patients. One reason may be the retention of the more able adult patients, which helps to keep down the cost of services. Doubtless a careful survey of patients would disclose a number whose seizures are under control and who might return to the family or the community and make way for patients more urgently in need of hospital care. Such a survey and resulting placements would require the professional help of social workers. At present the hospital staff and the 1400 patients have not a single social worker to help them in their multiplied social problems, although formerly Monson was adequately supplied — a circumstance that may account for the greater rate of discharge at one time. Doubtless each dollar spent in salary and adequate working conditions for competent social workers would save many dollars now lost through a stagnating pool of patients. A "total push" method of medical and social therapy would probably enlarge the outlets of the pool and permit the entrance of actively epileptic adult patients able to do the work of those discharged. During the past year, deaths numbered 54, and discharges 74. The total of 128 is approximately 10 per cent of the patients, which means residence for an average period of ten years, at a total cost per patient of at least \$5000, of which approximately \$250 is paid by the patient or his family.

However, the greatest long-range saving of money and release from the pressure of applicants should come from decreased need for institutionalization. As a money and health saver, prevention far out-

measures treatment, especially in epilepsy, in which a few capsules of medicine a day may mean the difference between social dependence and independence. Early diagnosis and institution of proper medical and social therapy for patients would prevent many a patient from ever entering Monson and becoming a public charge. Massachusetts has led the world in research, in drug therapy and in lay support of epileptic patients. In recognition of this fact, a National Veterans Epilepsy Center has been established at the Cushing Veterans Administration Hospital at Framingham. Establishment of a somewhat similar preventorium of chronic epilepsy and its sequelae near a center of medical influence for the short-term treatment, education or training of young persons of good intelligence would be a pioneer and profitable investment of public money. Contact with this group of patients, whose prognosis regarding both seizures and social usefulness is good, would increase the interest and the spirit of the medical, nursing and social-therapy staffs of Monson.

The second domain of importance for epilepsy and the most fundamental to the proper care of patients is the attitude of the general public. When the public realizes how much can be saved in dollars and in tears through medical research, through early and intelligent treatment of persons subject to seizures and through preventive measures intelligently applied (eugenics, better obstetrics, fewer childhood infections and fewer industrial, automobile and war injuries) enterprises now only dreams will quickly become facts. Experience has shown that public sentiment is changed only when groups of interested persons deadily in earnest get behind a program of enlightenment. This has happened for the epileptic patient in the organization of the American Epilepsy League, with an affiliated New England chapter with headquarters at 50 State Street, Boston. The New England Epilepsy League, which acts as a leaven in the otherwise unresponsive dough of public opinion, inspired the survey of Massachusetts doctors reported in this issue of the *Journal*, as well as a survey of all schools of higher education in the United States reported in the current issue of *Epilepsia*. It seeks to overcome prejudice among educators and employers and to aid phy-

sicians in their care of patients, whether private, clinic or institutional. It would lend its experience and knowledge to any broad-visioned, long-term plan for the prevention and better treatment of epilepsy, with consequent saving of both money and socially useful lives.

## THE NOLEN-MILES POUND LAW

ATTENTION is called to the communication by Dr. John Conlin, director of medical information and education of the Massachusetts Medical Society, which appears on the following page. It is of paramount interest to all physicians. Senate Bill 264 is pending before the General Court of the Commonwealth of Massachusetts. This legislation, entitled "An act to make available unclaimed and unredeemed animals impounded in animal pounds for scientific investigation, experiment or instruction" is of the utmost importance.

Medical schools and hospitals are facing a critical shortage of dogs and cats for experimental purposes. This is not a simple matter of fund raising or of passing financial difficulty. Animals are simply not available. It is incongruous that this situation should obtain while thousands of animals are destroyed annually in the public pounds. These animals, vagrants and strays, are condemned to death as a menace to the health of the community. How much better that some of them should have death deferred until under humane auspices they are used for studies contributing to the health and welfare of humanity and of animal pets!

A hearing on S. 264 will be conducted before the Committee on Legal Affairs at the Gardner Auditorium at the State House in Boston on Tuesday, February 24, at 10.30 a.m. It is a matter of the greatest importance that legislators be informed of the urgent and cogent reasons for the passage of this bill.

The Constitution of the Commonwealth, in Section II of Chapter V, states "Wisdom and knowledge, as well as virtue, diffused generally among the body of the people, being necessary for the preservation of their rights and liberties, and as these depend on spreading the opportunities and advantages of education in the various parts of the country, and

among the different orders of the people, it shall be the duty of legislatures and magistrates, in all future periods of this commonwealth, to cherish the interests of literature and the sciences, and all seminaries of them."

## A ROSE BY ANY OTHER NAME

THE ability to smell has been under investigation in New Haven, and certain revolutionary discoveries in this direction have been released by the Yale University News Bureau. The sensation of smell, apparently, does not come from chemical reactions set up within the olfactory organ by odorous substances that impinge upon it, but results rather from impulses sent out from the organ at extremely high frequencies, as from a radio transmitting station. Smell, because of highly scientific researches made with the common cockroach and the busy bee, has moved into the realm of radiation physics.

The high-frequency impulses emanating from the olfactory end organ, like one way radar waves, fall within a detectable range of 8 to 14 microns. Substances falling outside this range—such, presumably, as carbon monoxide—cannot be smelled by human beings.

The theory of this new concept of smelling is based on the idea that heat moves toward a source of coolness. The olfactory organ is 'hot', the odorous gas is "cool." As the sense organ loses heat the gas gains it, when a balance is reached we become insensitive to the odor. Further work is expected to establish a smell spectrum in which the four thousand to six thousand odors detected by the human nose can be plotted. Thus the guesswork can be removed from smelling.

Smelling distances have apparently not yet been measured, and such naïve predictions as "smelling to high Heaven" will presumably remain in the realm of the unexplored. Nor has the intransitive form of the verb received its full share of scientific recognition. Studies on the ability to smell in this sense remain commercial and seem still to be restricted to those exquisites of radio pronunciation, the foghorn voices that, in a perfectionism of vulgarity, suggest the employment of certain cleansing mediums in the interest of social acceptance.

for the hopeful patients tend to block the exits of the institution. The lives of imbecile children with brains undeveloped or irreparably damaged, whose only hope is death, are prolonged through the conscientious use of prophylactic inoculations against childhood infections. Thanks to the sulfonamides and penicillin, pneumonia is no longer the friend of the aged to the extent that it once was. Tuberculosis, formerly a 10 or 12 per cent contributor to death in institutions, is under control at Monson. A recent survey by means of chest films disclosed less tuberculosis than in the outside population.

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excruciating kind. Yet after long years it is admitted that no real progress has been made. If anything has been proved, it is the utter futility of all this shocking cruelty.

This is the same profound thinker who observed at a State House hearing a year ago

Insulin is a dangerous thing. A man who becomes addicted to it is a slave, more or less to the continuous treatments and all that. Some people assert that it has a very deleterious effect. The statistical tables are contradictory about it.

In the January, 1947, issue of *Living Tissue* appeared an interesting item captioned "The Oxford Case"

A sordid incident which should be "prescribed reading" for those who ignore the evils of vivisection and naively trust the word of those who defend it, is reported from no less a [sic] famous institution of learning and citadel of culture than Oxford University. It seems that Edward George Taody Liddell Professor of Physiology was convicted of cruelty to cats. *His appeal was disallowed* [italics mine]. Excerpts from a commentary on the case which appeared in the November issue of the English publication, *The Cat* follow

The excerpt stated that Professor Liddell was charged and convicted in May of cruelty to some thirty-six cats. The RSPCA was congratulated for prosecuting and winning the case.

A review of four clippings from the London *Times* helps to freshen the air. The last of these, under date of October 11, 1946, is most significant. It states that "none of the allegations at the Oxford City Quarter Sessions was proved against Dr Liddell except that of overcrowding and, therefore, he (The Recorder) would reduce the fine of £25 imposed by the city magistrates to £5." Even this patent sop to the antivivisectionists hardly warrants the language used in *Living Tissue*.

The New England Anti Vivisection Society has a particular fondness for quoting "the late Dr Henry J. Bigelow, Professor of Surgery at Harvard Medical School and long associated with the Massachusetts General Hospital." The "late" Henry Jacob Bigelow (1818-90), speaking of animal experimentation as he observed it at the Veterinary School at Alfort, France, some thirty years before the advent of ether anesthesia, stated before the Massachusetts Medical Society on June 7, 1871, "There will come a time when the world will look back to *modern* [italics mine] vivisection in the name of science as they now do to burning at the stake in the name of religion." The blithe disregard for the dictionary definitions of such terms as "late," "cruelty" and "torture" is rather characteristic of our opponents.

Another look at the record is in order. The "late" Dr. Bigelow wrote a letter to *Our Dumb Animals*, the publication of the M S P C A. This letter stated "The dissection of an animal in a state of insensibility is no more to be criticized than is the abrupt killing of it, to which no one objects. A painless experiment upon an animal is unobjectionable."

His son, William Sturgis Bigelow, wrote in a letter to the Editor of the *Boston Herald* on December 13, 1921

My father was extremely active in securing the physiological laboratory for Harvard University. He did as much as anybody to secure that very laboratory, where then, and now, animal experimentation is carried on when necessary and where results have been obtained which have been of vital benefit to the human race.

The dentist Morton first tested ether on his dog. Walter B. Cannon, pioneer in x-ray examination of the alimentary tract, worked with a bismuth salt on cats. The surgery of Elliott C. Cutler on the valves of the heart and the work of Lennox in epilepsy, of Gross in congenital heart defects and of Harken in wartime wounds of the heart and great vessels would have been impossible without the contributions of animal research in Massachusetts.

Our opponents state that only relatively few physicians have any stake in animal experimentation. This clever "divide and rule" stratagem must be strongly opposed. In our writings the background of animal studies should be stated. Our speakers must stress this vital subject. And above all our patients must be informed. It takes but a moment to tell the animal background of such drugs as digitalis, adrenalin, Dilantin and the rest.

A bill has been filed before the Massachusetts legislature. The Nolen-Miles Pound Law, Senate Bill 264, is pending before the Committee on Legal Affairs. This bill will make unclaimed and unredeemed animals from public pounds available for medical teaching and research. Pets given over to animal pounds for execution are excluded from the provisions of the bill. The six-day period provided by law for the recovery of lost pets is maintained.

Relatively few of the thousands of dogs and cats executed annually in local pounds are required by our medical schools and hospitals. These will be humanely treated. It is their privilege to serve as the K9-corps dogs did in wartime—for the protection of their human masters. Benefits will be obtained that are for the preservation of life and the relief of suffering of both man and animal.

We have repeatedly justified our conduct of the priceless privilege and heritage of animal experimentation. No law has been passed to restrict our humane teaching and research. We can no longer continue our necessary work without extreme difficulty and unwarranted expense. We appear before the legislature with clean hands and unselfish motives.

Our opponents profess to be humanitarians. They would protect and benefit the dog and cat. Our higher humanitarian sentiments must prevail. We protect and benefit the dog, the cat and the human being.

JOHN F. CONLIN, M.D.  
Director of Medical Information and Education,  
Massachusetts Medical Society, chairman, Massachusetts  
Society for Medical Research



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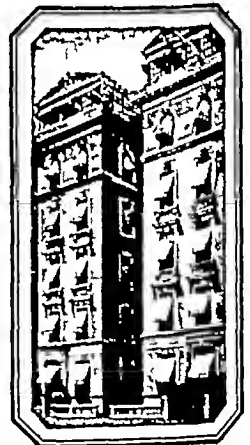
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## WHICH TYPE CESAREAN SECTION?\*

ROY J. HEFFERNAN, M.D.,† AND CHARLES LEAVITT SULLIVAN, M.D.‡

BROOKLINE, MASSACHUSETTS

ABDOMINAL delivery may be accomplished in one of three ways by the classic technic, by the low-segment operation or by some form of extra peritoneal cesarean section. It is not possible to compare absolutely the safety of the various procedures because of the variance in skill of individual operators and hospital equipment and also because the results reported by individual operators and clinics are not standardized so far as the condition of the patient at the time a particular technic was chosen for abdominal delivery is concerned.

The classic method results in the highest morbidity and mortality because the uterine incision is the only barrier between the peritoneal cavity and the interior of the uterus, which, as repeated studies have shown, may be invaded by pathogenic bacteria soon after delivery. The classic technic tends to form more adhesions than the other types, and rupture of the uterus occurs more frequently in subsequent pregnancies. The low-cervical operation has a better record. With the development of a bladder flap there is a double barrier to the spread of infected uterine contents. The uterine incision is well covered by peritoneum, adhesions are less likely to form, and the incidence of future rupture is less. We have collected a series of 14,776 low-segment operations reported in the literature in which the mortality was 1.52 per cent, whereas 15,030 patients subjected to classic sections by the same operators and under similar hospital conditions had a mortality of 3.87 per cent (Table 1). It is therefore apparent that, in general, the low-segment operation is over twice as safe as the classic and has fewer subsequent complications. These figures are even more impressive when it is considered that the low-segment operation was frequently selected because the patient was potentially infected. The low-segment or low-cervical cesarean section is usually a safe and satisfactory procedure

when done electively, when patients have been in labor for ten hours or less, with intact membranes, and when there have been no vaginal examinations. Since the incision in the uterus can be thoroughly

TABLE 1 Mortality in Low-Cervical Compared with That in Classic Section

AUTHOR	LOW CERVICAL SECTION		CLASSIC SECTION	
	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY
Steel and Jordan <sup>1</sup>	108	2.8	827	7.6
Phaneuf	166	0.6		
Montgomery <sup>2</sup>	33	3.1	180	5.5
Sehara <sup>3</sup>	724	2.7	103	4.9
Greenhill <sup>4</sup>	108	0.0		
Lail <sup>5</sup>	103	3.8	478	6.7
Waters and Leavitt <sup>6</sup>	116	4.2	333	5.7
Seely <sup>7</sup>	87	0.0	105	7.6
Daily <sup>8</sup>	461	0.6	8	5.0
McNeill <sup>9</sup>	165	0.0	113	6.1
O'Connor <sup>10</sup>	133	5.3	406	4.0
Court and Fletcher <sup>11</sup>	376	1.3	6.3	7.7
Arnold <sup>12</sup>	204	0.0	131	4.6
Carroll <sup>13</sup>			107	1.9
Beckley <sup>14</sup>	183	2.7	116	14.6
Gernia et al.	131	0.0		
Thompson et al. <sup>15</sup>	253	1.2	618	3.6
Stude <sup>16</sup>	4	0.0	70	5.7
Barrett <sup>17</sup>	620	0.8	235	3.4
DeNormandie <sup>18</sup>	111	2.6	40	3.2
DeLee <sup>19</sup>	541	2.0	490	5.5
DeLee <sup>20</sup>	1675	0.9	168	6.0
Ryder <sup>21</sup>	100	2.0	218	0.9
Lazarus <sup>22</sup>	241	0.4	54	9.3
Grafston <sup>23</sup>	208	0.9		
Irvine <sup>24</sup>	686	0.9	1031	1.3
Falk <sup>25</sup>	57	0.0	57	1.7
Gustafson <sup>26</sup>	135	3.7	226	8.4
Matthews et al. <sup>27</sup>	261	1.8	737	3.9
Matthews et al. <sup>28</sup>	218	1.8	894	1.7
Rosenrohn et al. <sup>29</sup>	215	2.3	255	3.9
Kings <sup>30</sup>	488	3.3	645	7.1
Lail <sup>31</sup>	324	1.2	550	3.0
Hawley <sup>32</sup>	30	0.0	492	4.0
DeNormandie <sup>33</sup>	1336	1.2	1009	2.9
DeNormandie <sup>34</sup>	1207	2.1	934	2.5
DeNormandie <sup>35</sup>	1003	2.3	898	2.9
Quigley <sup>36</sup>	196	1.0	717	3.3
Falk <sup>37</sup>	142	0.0	122	1.6
Heffernan <sup>38</sup>	150	0.0		
Totals	14776		15030	
Percentage mortality		1.52		3.87

covered by peritoneum there is very little danger of peritonitis. But, when the membranes have been ruptured or labor has been in progress for several hours or when there have been any vaginal or any rectal examinations, any form of intraperitoneal cesarean section may be fraught with danger, and

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1947.

†Harvard Medical School, Tufts College Medical School, and Boston College of Obstetrics and Gynecology, Carney Hospital, consulting gynecologist and obstetrician, Faulkner and St. Margaret's Hospital.

‡Assistant obstetrician, Massachusetts General and St. Elizabeth's Hospitals.

in such cases the lower-segment operation does not offer sufficient protection against peritonitis

Seventy-five per cent of deaths from cesarean section occur from infection or hemorrhage, and the remainder from the complications of major surgery or conditions existing prior to the section and possibly aggravated by it. Peritonitis can occur without hemorrhage, which, when present,

TABLE 2 *Cesarean Hysterectomy for Infection*

AUTHOR	NO OF CASES	NO OF DEATHS
Greenhill <sup>12</sup>	1	0
Hawks <sup>22</sup>	2	1
Lash and Cummings <sup>23</sup>	12	4
Adair <sup>24</sup>	5	0
Phaneuf <sup>25</sup>	7	0
Lazard <sup>26</sup>	9	0
Daily <sup>27</sup>	30	2
Maxwell <sup>28</sup>	2	1
Arnot <sup>29</sup>	10	2
Briscoe <sup>30</sup>	3	3
Wilson <sup>31</sup>	9	0
Stude <sup>32</sup>	2	1
Irving <sup>33</sup>	21	3
Falls <sup>34</sup>	2	0
Totals	119	17 (14.2%)

always predisposes to infection. The advances of chemotherapy and the development of the antibiotics will control most infections, but mothers still die from peritonitis in spite of adequate treatment by these agents. Many of these patients have been attacked by organisms, such as the anaerobic nonhemolytic streptococcus, that are resistant to these drugs. In a series of 1887 cesarean sections

TABLE 3 *Extraperitoneal Latzko Cesarean Section*

AUTHOR	NO OF CASES	NO OF DEATHS
Cosgrove <sup>35</sup>	74	2
Steele <sup>36</sup>	59	5
Aldridge <sup>37</sup>	27	1
Hawks <sup>38</sup>	30	0
Irwin <sup>39</sup>	285	9
Burns <sup>40</sup>	79	2
Sackett <sup>41</sup>	51	4
Perrins <sup>42</sup>	22	0
Holtermann <sup>43</sup>	194	10
Norton <sup>44</sup>	26	0
Fleischer and Kushner <sup>45</sup>	19	0
DeNormandie <sup>46</sup>	13	0
DeNormandie <sup>47</sup>	33	2
Irving <sup>48</sup>	40	1
Waters <sup>49</sup>	193	3
Totals	1145	39 (3.4%)

reported by Irving<sup>25</sup> from the Boston Lying-in Hospital, covering a period of ten years from 1934 to 1943, 42 per cent of the total number of deaths were due to peritonitis.

When actual signs of infection, such as fever, a rapid pulse and a foul amniotic discharge, are present before delivery, any type of transperitoneal section is definitely contraindicated. In 1933 DeLee<sup>40</sup>

wrote "My opinion is firm laparotrachelotomy for all, but in those where infection is suspected, then Latzkos, Porro, or craniotomy."

To consider these procedures in reverse order, craniotomy on the living child is mentioned only to be vehemently condemned. It has no place in modern obstetrics, and the claim that sacrifice of the baby saves the mother is disproved by the experience of Baird,<sup>41</sup> who reports a maternal mortality of 7 per cent in 147 cases of craniotomy. Cesarean hysterectomy for infection adds operative shock and additional blood loss to that of a cesarean section, and if the patient is a young primipara the loss of the uterus may indeed be tragic. We have collected from the literature a series of 119 cesarean hysterectomies done for infection, with a mortality of 14.2 per cent (Table 2). We believe that cesarean

TABLE 4 *Modern Extraperitoneal Cesarean Section*

AUTHOR	NO OF CASES	NO OF DEATHS	DEATHS FROM SEPSIS	DEATHS FROM HEMORRHAGE
Norton <sup>50</sup>	160	3	2	1
Ricci and Marr <sup>51</sup>	175	1	0	1
Irwin <sup>52</sup>	32	0	0	0
Pieri and Irving <sup>53</sup>	20	0	0	0
Essaman and Austin <sup>54</sup>	22	0	0	0
Williamson and Goldblatt <sup>55</sup>	25	0	0	0
Daichman and Pomerance <sup>56</sup>	100	0	0	0
Bowles <sup>57</sup>	10	0	0	0
Burgeois <sup>58</sup>	10	0	0	0
Briscoe <sup>59</sup>	9	0	0	0
Stearns <sup>60</sup>	16	0	0	0
Cross <sup>61</sup>	89	1	1	0
Irving <sup>62</sup>	59	2	-	-
Waters <sup>63</sup>	290	2	1	-
Heffernan and Sullivan	72	0	0	0
Totals	1089	9 (0.82%)	4	2

hysterectomy has no place in the treatment of infected patients and should be reserved for parturient patients with fibroids, atonic uteri or other pathologic conditions of the uterus.

Although the morbidity and mortality for abdominal delivery in cases of infection, both potential and actual, have improved since the advent of the antibiotics, chemotherapy and well stocked blood banks, the relative safety of the classic, low-segment and extraperitoneal types of section remains the same. When potential or actual infection exists neither the classic nor the lower-segment operation, even with the antibiotics and chemotherapy, affords the patient the full measure of protection.

The extraperitoneal approach, the principles of which were first expounded over a hundred years ago, is the safest method of abdominal delivery. In 1821 Ritgen<sup>51</sup> first tried to approach the lower anterior extraperitoneal surface of the uterus from the lateral aspect of the bladder through the paravesical space. Fundamentally the operations of Baudeloque,<sup>52</sup> Thomas<sup>53</sup> and Latzko<sup>54, 55</sup> fall into the same group. The commonly accepted technic, until the presentation of Waters<sup>56</sup> and Ricci,<sup>57</sup> was

that described by Latzko. We have collected from the literature a series of 1145 cases in which Latzko sections were performed, with a mortality of 3.4 per cent (Table 3). Although, as noted by the authors, the collections of classic and low-segment operations contained an admixture of clean, potentially infected and infected cases it is probable that this series consisted entirely of potentially in-

The modern concept of the extraperitoneal approach lies in the principle first expounded by Physick of Philadelphia to DeWees<sup>66</sup> in Horner's letter in 1824. This suprapubic approach was not attempted until Frank<sup>66</sup> and later Sellheim<sup>70</sup> unsuccessfully tried it. The same approach is the basis for a series of operations presented by Waters<sup>68</sup> in January, 1939, with one radical difference: the

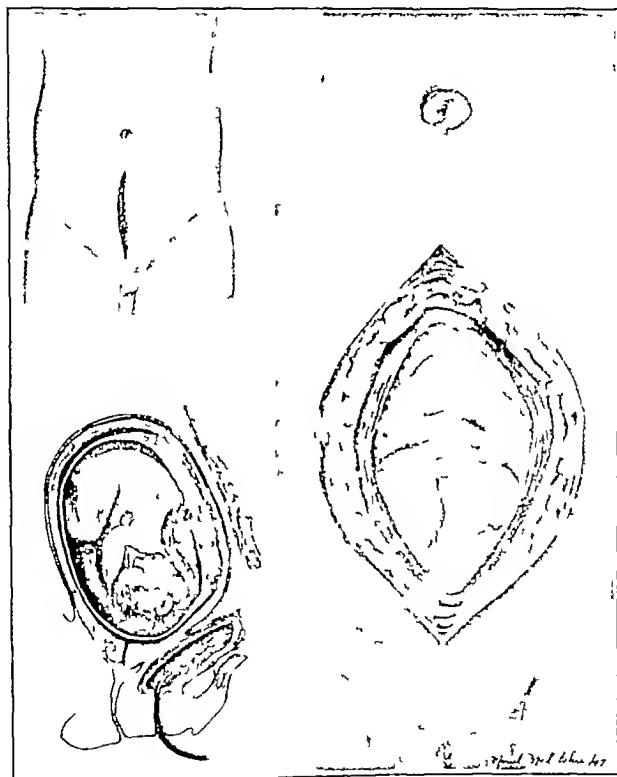


FIGURE 1

*The upper left illustration demonstrates a low suprapubic incision (extending from 5 cm. below the umbilicus to the pubis)*

*The lower left illustration shows a sagittal view (the double lines indicate peritoneal reflections)*

*The right illustration demonstrates an incision to the transversalis fascia showing separated recti and a distended bladder*

fectured cases. Nevertheless, the mortality was less than that in cases in which the classic technic was used. However, the Latzko operation was always difficult and rarely presented an adequate space through which the baby could be delivered, and tears of the peritoneum and injuries to the ureters, bladder and uterine vessels frequently occurred.

plane of dissection. Previous operators had attempted to peel the peritoneum from the bladder and pelvic fascia, and Waters showed that the proper technic was to lift the peritoneofascial flap as a unit. Ricci and Marr,<sup>71</sup> in an excellent monograph, present a clear description of the anatomy of the area, as well as a detailed discussion of their

method Norton<sup>72</sup> describes a procedure that lies between the old Latzko operation and the methods of Ricci and Marr and Waters, in that the bladder is not completely separated from the peritoneal fold, the approach being paravesical and the dis-

effect by keeping it localized to the uterus. Naturally, the antibiotics and chemotherapy are employed when indicated.

In 1942 we began to use this operation in actually or potentially infected patients, and we have been so impressed with its value that we frequently employ it now in clean, elective cases. Figures 1 to 8 outline the salient features of the technic.

Although any anesthetic may be used, we have preferred small doses of spinal anesthesia—the

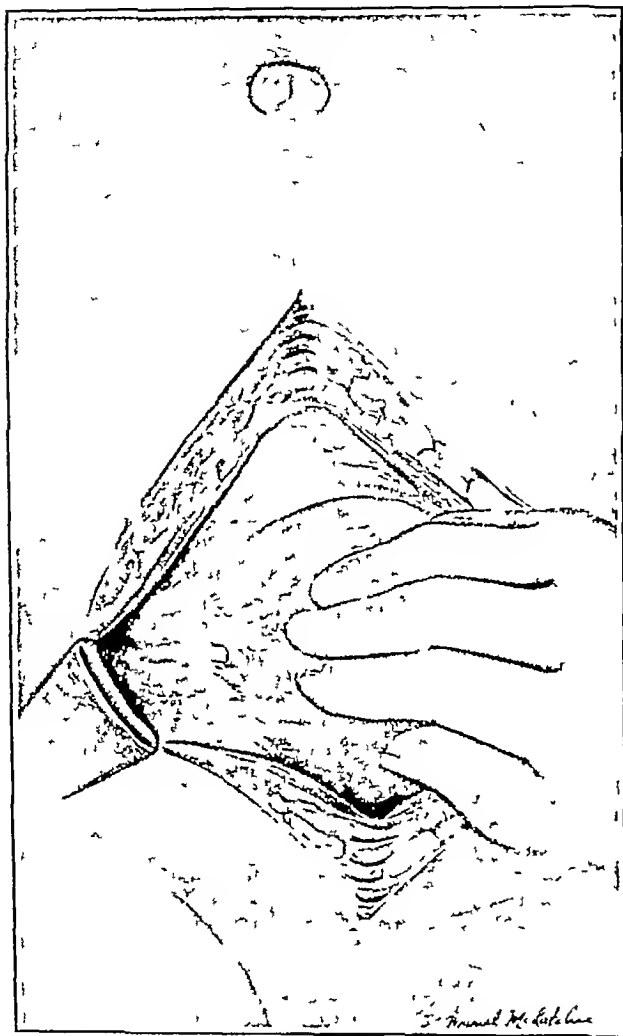


FIGURE 2 Right Rectus Muscle Retracted Laterally, Exposing the Paravesical, Yellow, Chicken Fat Pad, Lateral to the Base of the Bladder

placement medial. The approach today involves either the complete or incomplete dislocation of the bladder from its lower-segment bed, its displacement downward or medially after complete or incomplete separation from the peritoneal fold, resulting in an adequate extraperitoneal approach to the lower uterine segment. Since the first presentation of this modern method we have been able to collect from the literature a series of 1089 cases of extraperitoneal cesarean section with a mortality of 0.8 per cent (Table 4). It is important to note that there were deaths from sepsis. It is clear, then, that this operation is not offered as a cure for infection, but rather to prevent the spread of actual or potential infection and to minimize its

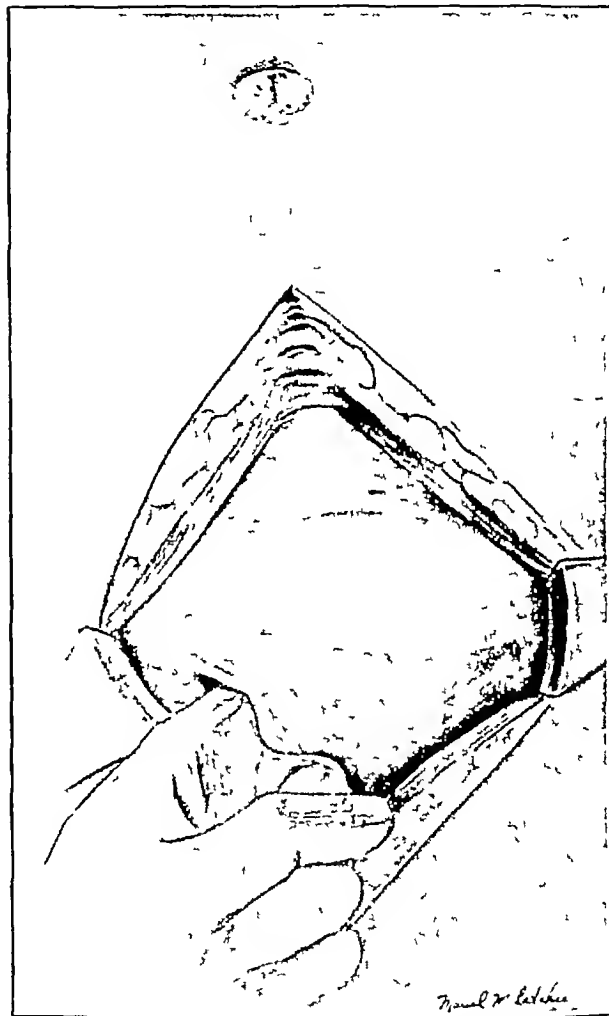


FIGURE 3 Paravesical Fascia and Fat Pad Separated and Finger Inserted between the Posterior Surface of the Bladder and the Lower Uterine Segment (the Procedure is Repeated on the Other Side)

danger of doses of average size in obstetrics is too little realized, and we urge the selection not only of a competent anesthetist but also of a minimal dose of the drugs employed. We use 50 mg of novocain crystals and 5 mg of pontocaine in 2 cc of spinal fluid. Injection is made in the fourth interspace without barbiturates, unless the operation is prolonged for any reason, when a small amount of

intravenous barbiturate or inhalation anesthesia may be used as a supplement.

We have made use of this operation in 72 cases to date, and in our experience there has been no fetal or maternal mortality. The most impressive feature, however, has been the complete absence of postoperative morbidity. Such patients may eat within six hours of operation and have no nausea, no vomiting or "gas pains" and no more distention than occurs after a normal delivery from below. When indicated ambulation may be permitted as soon as the effect of the anesthesia has subsided.

As we grew familiar with this technic and realized through experience that the operation itself presented no hazard to the mother we gradually

*Ruptured membranes.* The procedure is indicated in any case in which the membranes have been ruptured for a period of eight hours. Although this duration is arbitrary, amniotic infec-

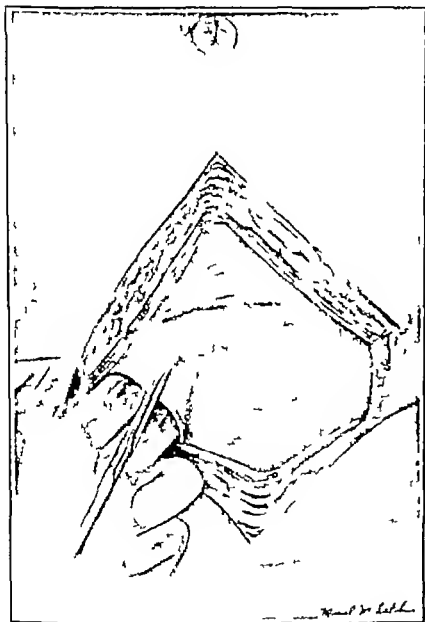


FIGURE 4. Incision Started through the Transversalis Fascia below the Peritoneal Reflection

widened our scope of indications, and at the present time we use it for the following conditions:

*Infection.* We consider the operation indicated in any patient in whom there is the slightest suspicion of infection, either genital or extra-genital. Dehydration fever can easily be diagnosed and eliminated by proper treatment.

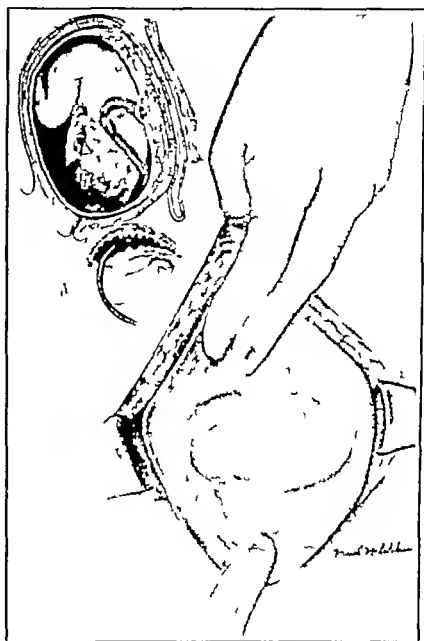


FIGURE 5. Lower Uterine Segment Exposed—Peritoneofascial Fold Retracted Upward, Bladder Mobilized and Drawn Downward

The sagittal view shows the lower uterine segment exposed extraperitoneally. The double line indicates the peritoneal fold now completely separated from the bladder.

tion may be present in an early stage without systemic reaction.

*Labor.* Actual infection of the uterine cavity potentially starts with the onset of labor, and there is no method of absolutely eliminating cases that are free of infection. Any patient in labor for six hours or longer should have the added insurance of this procedure. Harris and Brown<sup>22</sup> found no sterile cultures of the lower uterine segment at operation when labor had lasted six hours or more.

*Vaginal examination.* The operation is performed in patients who have had vaginal examinations or repeated rectal examinations.

*Unsuccessful trial at pelvic delivery* When it is found that an attempted forceps operation can be concluded only with serious damage to the mother or the baby, or both, the forceps should be removed, and an extraperitoneal cesarean section performed. Irving<sup>25</sup> has shown that

qualities, such as those suffering from malnutrition or avitaminosis, are best protected by the extraperitoneal approach to prevent wound dehiscence and evisceration with its attendant high mortality—an event occurring in about 1 in 600 cases.<sup>25</sup>

Patients at or near term, when the lower uterine segment is well developed, are the best subjects for this operation. We have done the operation as early as thirty-one weeks. It can be performed with ease on patients not in labor. Drainage is performed only in patients believed to be actually

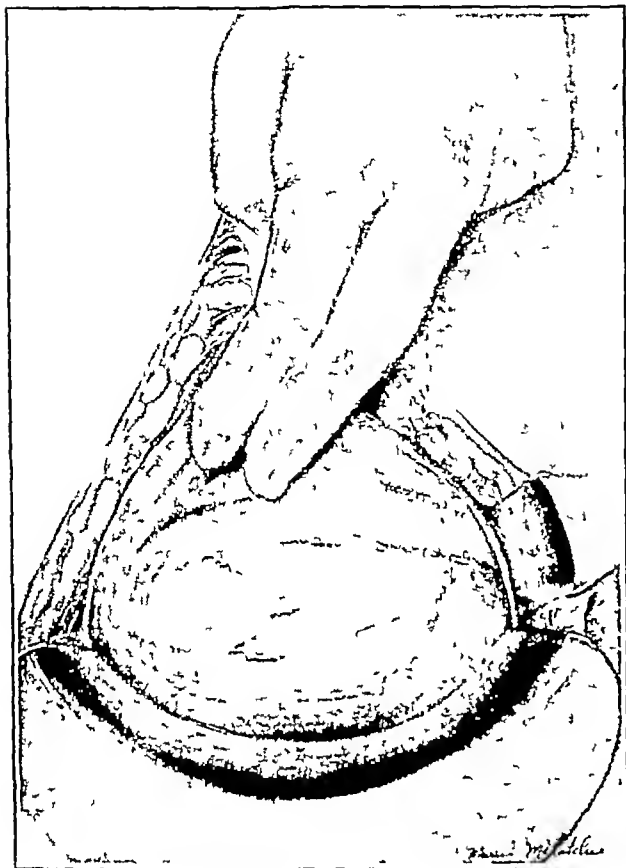


FIGURE 6

*Transverse incision in the thin layer of the anterior uterine fascia permits the peritoneofascial fold to be displaced cephalad. This allows adequate exposure to the lower uterine segment, even though the patient has not been in labor. The bladder has dropped beneath the symphysis-Doyen retractor shown in position.*

at the Boston Lying-in Hospital a difficult mid-forceps operation can be almost as dangerous to the mother as an intraperitoneal cesarean section—and about eight times more dangerous to the baby.

*Previous phlebitis or extensive varicosities* Earlier ambulation after the extraperitoneal operation is a definite advantage in the patient with a history of previous phlebitis and extensive varicosities.

*Poor surgical risks* This category includes all patients generally regarded as poor surgical risks—that is, those with chronic respiratory infection or severe pre-eclampsia. The correlation between blood loss and sepsis is well known, and we have done this operation in placenta previa and separated placenta with this thought in mind. Patients suspected of poor healing

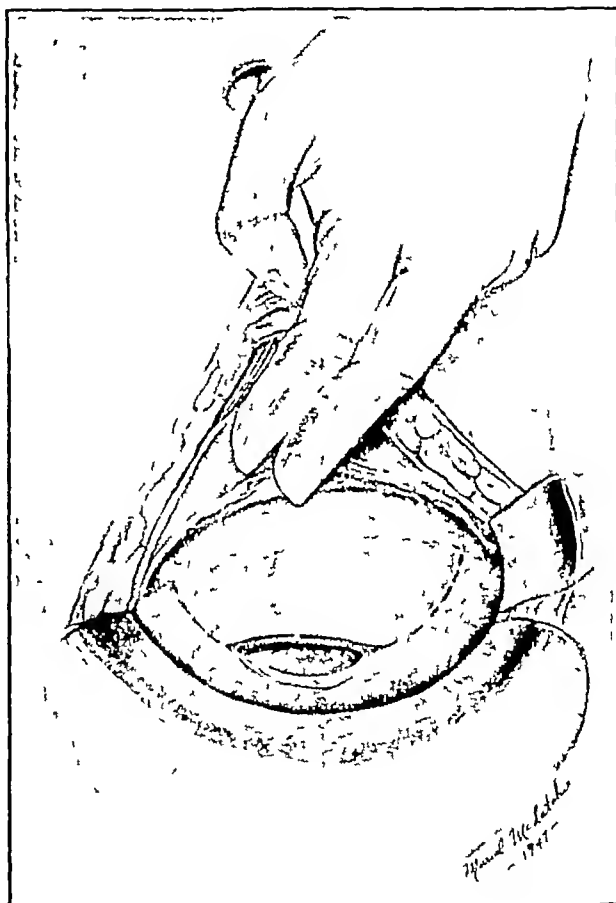


FIGURE 7 *Curved Incision of Lower Uterine Segment Started, Exposing Amniotic Sac. Note the pronounced convexity.*

infected, a “fish-tail” drain being applied to the uterine incision, this is withdrawn on the fifth day. The bladder is placed on constant drainage for a period of twenty-four hours, after which all patients have been able to void spontaneously without retention.

#### SUMMARY

Although better obstetric management, improved operative technic, replacement of blood loss and the

advent of chemotherapy and the antibiotics have considerably lowered the incidence of peritonitis after cesarean section, the complication still occurs, especially after the classic procedure. This type of abdominal delivery has so many disadvantages that

classic, it is not without danger in the potentially infected case, since it does not ensure protection against peritonitis from the spill or seepage of infected uterine contents.

Craniotomy on the living child is never justifiable

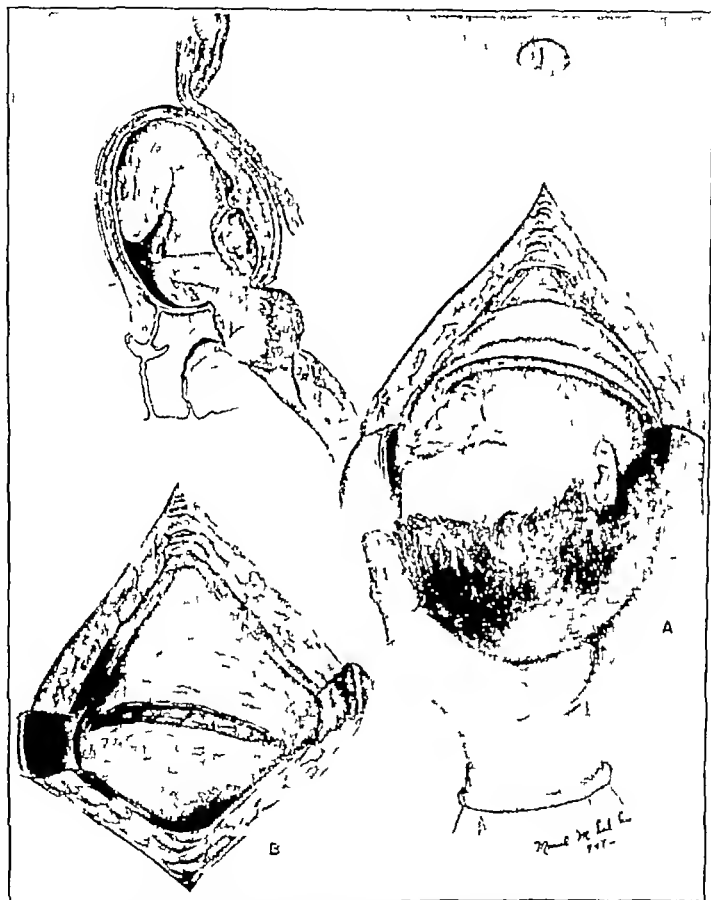


FIGURE 8. *Sagittal view Demonstrating Extraperitoneal Extraction Effected by the Use of the Fingers as a Tactus Assisted by Suprafundic Pressure*

A shows a similar anterior view

B shows the uterine incision closed and the bladder re-filled to check integrity

it should be used only when better methods are not applicable or when the uterus is to be removed.

The lower-segment operation is a very satisfactory type of abdominal delivery in uncomplicated, clean cases, and although over two times safer than the

Cesarean hysterectomy should be used only when some pathologic condition necessitates the removal of the uterus.

The modern extraperitoneal operation not only is the safest technic for the infected or potentially



infected parturient patient but also may be used to advantage for less imperative indications

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## THE WORK OF A PHYSICAL-FITNESS CLINIC

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THIS is a report of a physical-fitness clinic conducted at the Massachusetts headquarters of the Blue Cross among approximately 900 executives and employees

The personnel conducting the clinic consisted of one experienced physical-fitness worker, three physicians, part time, especially trained to make physical examinations to detect not only disease but also any physical defects that might cause impaired health, and a secretary trained in statistics, to tabulate results and to act as receptionist and make appointments. I supervised the work and saw problem cases one morning each week.

The physical-fitness worker and the secretary were on full time. One of the three part-time physician worked six hours a day for one day and three hours a day for four days each week.

## PROCEDURE

Every applicant to the clinic was given a health examination, with the object of identifying the causes of impaired health. This examination was uniform, over a hundred factors relating to the causes of health impairment being checked.

The examination consisted of a health history of the applicant, a check-up of twenty of the most common faulty health habits, a check-up of the daily program for twenty-four hours in a typical day, a check-up of all food taken in a twenty-four-hour period and a physical examination to detect not only actual disease but also any physical defects that might impair health.

The time given to each health examination and directions for the correction of both physical defects and faulty health habits was exactly sixty-five minutes. Two applicants were examined each hour, or 36 a week. The remaining time of the physical fitness worker was devoted to return visits, especially to those who were in the danger zones of overweight and underweight. Because of the relation of weight to mortality, recognized in insurance work by rejection or substandard ratings on this factor alone, the group was separated into three divisions: overweight, optimum weight and underweight.

The optimum weight zone was determined by the range of lowest mortality found in the *Medico-Actuarial Table* of 1912 (Fig 1). This zone extends approximately from 5 to 15 per cent above average weight and closely corresponds with that determined by clinical standards and individual health experience. Overweight includes those above optimum

weight, and underweight those below optimum weight.

## WEIGHT STATUS

In a period of approximately six months, 735 executives and employees, seventeen to sixty-three years of age, received this health service. The findings are presented in Table 1.

## FAULTY HEALTH HABITS

Health habits that deprived the subject of one or more of the essentials of health — namely, fresh air and sunlight, proper food and food habits, regular exercise and proper rest — were considered faulty. To these must be added regularity of living habits, which is a fundamental factor in acquiring physical fitness.

The faulty health habits found by a check-up on each applicant are presented in Table 2.

The faulty health habits found in each weight zone are presented in Table 3, which demonstrates that applicants of normal weight had fewer faulty health habits than either the overweight or the underweight subjects. The most frequent faulty habits of the overweight applicants were no regular rest periods, insufficient exercise and outdoor sunlight, fast eating, habitual overeating and candy between meals. Those of the underweight group were no regular rest periods, insufficient exercise and outdoor sunlight, fast eating, candy between meals and irregular bedtime.

## PHYSICAL DEFECTS

The physical defects found are presented in Table 4. Each employee was referred to his own physician or dentist for defects needing correction. Thus, 197 (27 per cent) applicants were referred to family physicians, and 124 (17 per cent) to family dentists.

When his faulty health habits had been checked and the physical examination completed, the applicant was told what health habits and what physical defects were found, and their effect in impairing his health was explained. He was also told that both overweight and underweight were unnecessary and that by correcting his habits that were essentially faulty he could improve his health and thus add years to his period of active work and efficiency.

He was then asked this question: "Are you interested in planning your day's activities to correct these defects and to work for better health?" If he said he was interested, it was suggested that he weigh in each week, and he was told that he would be helped to plan his daily program to attain better health.

\*Director, Physical Fitness Clinic, Blue Cross, formerly director, Physical Fitness Clinic, The Life Insurance Company and Dartmouth College.

## RETURN VISITS

After the examination had been completed, the applicant was offered an opportunity to return each

735 applicants taking the service answered "No" Yet, when their daily programs were checked up, a total of 2294 faulty health habits were found — an average of 3 1 habits that needed to be corrected

The response to the offer of an opportunity for return visits was so great that soon it became necessary to reduce the number of initial examinations to take care of the return visits In the limited time of the demonstration, the number of return visits

TABLE 2 Faulty Health Habits (All Applicants)

FAULTY HEALTH HABITS	NO OF CASES	PER CENTAGE
No regular rest periods	717	98
Insufficient exercise or outdoor sunlight	273	37
Fast eating or washing down food	205	28
Candy or sweets between meals	165	22
Worry and fretfulness	143	19
Removable physical defects uncorrected	128	17
Habitual overeating or undereating	114	16
Irregular bedtime	112	15
Irregular time of bowel movement	105	14
Irregular habits of living	71	10
Excessive use of tea, coffee, alcohol or tobacco	59	8
Excessive fastidiousness about food	47	6
Sleeping with windows closed	41	6
Overdoing at work or play	39	5
Irregular mealtimes	32	4
Eating when overtired	19	3
Inadequate vacations or weekly rest	10	1
Uncontrolled likes and dislikes	8	1
Habits injurious to health	5	1
Working in poor air (above 68°)	0	0
Total	2294	
Average		3 1

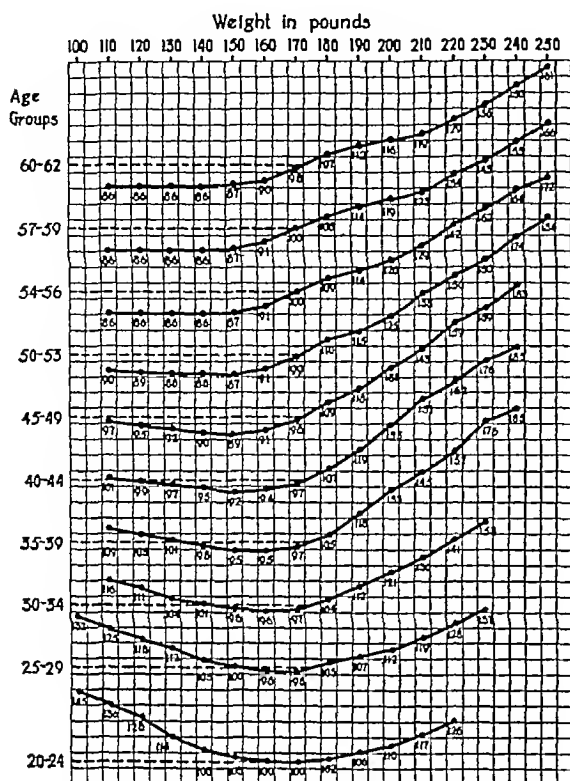


FIGURE 1 Influence of Weight on Mortality

The figures on the curves represent the percentage of mortality for the respective ages and weights. In the early twenties mortality increases about 1 or 2 per cent below average weight for height. Above the age of thirty-five mortality increases a like percentage for each pound above optimum weight (Reproduced from Emerson<sup>1</sup>)

week for suggestions regarding the most efficient way to gain or lose weight and how to make changes in his daily program of activities to correct

TABLE 1 Weights of 735 Men and Women

STATUS OF SUBJECTS	RANGE	NO OF CASES	PER CENTAGE
	lb		
186 men			
Overweight	2-64	46	25
Normal weight	—	50	27
Underweight	1-35	90	48
549 women			
Overweight	1-103	118	22
Normal weight	—	189	34
Underweight	1-34	242	44
735 men and women			
Overweight	1-103	164	22
Normal weight	—	239	33
Underweight	1-35	332	45

faulty health habits and secure the essentials of health

In answer to the question, "Have you any health habits that are injurious to your health," 730 of the

made by those interested in working for a higher standard of health was 2822

At each return visit, the applicant was weighed and his diet list checked, and suggestions were made

TABLE 3 Faulty Health Habits According to Weight of Applicant

STATUS OF APPLICANTS	NO OF CASES	FAULTY HEALTH HABITS	
		NO OF CASES	AVERAGE
Overweight	164	559	3 40
Normal weight	239	687	2 87
Underweight	332	1048	3 15
Totals	735	2294	
Average			3 10

for rearranging his daily program to ensure him essentials of health

The time given for each return visit from the time of entering the clinic to the time of leaving was an average of eight minutes

In this demonstration, as elsewhere, the return visits were found to be of great importance, because habits of daily living are determined not by the requirements of healthful living but by individual family life, working conditions, social life and diver-

sions that, from the standpoint of health, may be dissipations

Directions for improving health were given by the physician and physical-fitness worker together, on the basis of the findings recorded on the examination form. Directions were given as definitely as those given by the physician after he makes a diagnosis of disease.

The success of the applicant in gaining or losing weight, in reducing his blood pressure and in increased efficiency and improvement in general well being kept him returning to the clinic until his objective had been attained. He was made to understand that the job was his, and that better health could be won only by his own efforts.

## RESULTS

### Overweight Applicants

It was suggested to the overweight applicants that they reduce their weight slowly, the reduction not to exceed an average of 1 or 2 pounds a week until they got out of the danger zone of overweight indicated in Figure 1 — the men, until the abdomen ceased to be prominent and the women, until the folds of fat disappeared from about the waist and hips.

The weight reduction accomplished in the limited time of the demonstration varied from 2 to 27 pounds, a total of 574 pounds.

The following case provides an example.

J. M., a 19-year-old girl had always been overweight and retained being called fat. She had tried various methods of reducing her weight without success. By reducing her diet (calories) to a point where she lost about 15 pounds a week she reduced her weight 27.5 pounds. During that time, she did not suffer from hunger after the 1st week and considered the diet that met her needs no special hardship.

### Underweight Applicants

The underweight applicants were found to have more faulty health habits than either of the other groups. Their daily programs showed almost continuous nervous tension, caused not so much by the pressure of work as by continuous activities outside working hours and on Saturdays and Sundays.

Their gain in weight during the time of the demonstration ranged from 2 to 14 pounds, a total of 246 pounds.

An example is afforded by the following case.

E. C., a 19-year-old girl was attractive and ambitious. She was working overtime 1 or 2 nights a week and studying designing 2 nights a week. She had no physical defects. Her faulty health habits were those of taking no rest periods during the long day and taking a light breakfast and a light lunch, and eating a hearty dinner at night when overtired. She was advised to take a complete rest lying down for 20 minutes before her evening meal and on Saturdays and Sundays to have her breakfast at the regular time, resting in bed until noon and utilizing the afternoon for outdoor exercise and sunlight. She was able to continue night and overtime work and gained 14 pounds — attaining normal weight for her height.

### Hypertensive Applicants

There were 12 cases of hypertension, the blood pressure ranging from 150 to 210 systolic and from 90 to 110 diastolic.

By loss of excessive weight and relief of high-pressure living by twenty-minute periods of complete rest before the evening meal, and by correction

TABLE 4 Physical Defects Discovered

DEFECT	NO. OF CASES
Underweight	332
Overweight	164
Fronted feet	154
Carious teeth	239
Nasopharyngeal obstruction	73
Spinal curvature	24
Acne	18
Malocclusion	12
Hernia	6
Varicose veins	4
Nasal polypus	3
Bronchitis	3
Furunculosis	3
Dermatitis	2
Psoriasis	2
Sonboes	2
Fungus inflammation of feet	2
Sinusitis	2
Chronic otitis media	2
Conjunctivitis	2
Hypertrophied tonsils	2
Hemorrhoids	2
Varices	2
Epithelial cyst	2
Rings worms	1
Keratitis	1
Pterygium	1
Blepharitis	1
Gout	1
Arrested tuberculosis	1
Perforated eardrum	1
Hay fever	1
French mouth	1
Appendicitis	1
Scomatosis	1
Valvular heart disease	1
Rheumatoid arthritis	1
Spinal arthritis	1
Total	972
Average	13

of faulty health habits, the reduction in systolic blood pressure averaged 20.

The faulty health habits in these cases were those of habitual nervous tension, insufficient exercise and outdoor sunlight and fast eating.

The following cases are illustrative.

H. M., a 56-year-old man weighed 191 pounds. He had recovered from a heart attack but was short of breath on slight exertion. His heart area was enlarged and a systolic heart murmur was heard over the entire pericardium. His faulty health habits were habitual overeating, worry, no rest periods and the candy habit.

He reduced his weight 13 pounds and his systolic blood pressure from 210 to 146. He was able to continue his regular work without untoward symptoms. In the meantime he was referred to his own physician for a more careful supervision of his heart condition.

D. R., a 50-year-old woman weighed 159 pounds. Her blood pressure was 150/50. She reduced her weight 25 pounds and her blood pressure returned to the normal of 116/82.

These findings and results closely parallel those observed in a group of 100 consecutive cases of hypertension reported in September, 1938.

### *Absenteeism*

All executives and employees were circularized before the work began. Therefore, an adequate control group was not available to compare days off from sickness.

However, a study of 100 employees taking the service and of 100 before taking the service (matched by five-year age ranges, by sex — 26 women and 24 men — and to some extent by employment status) showed a reduction of 26 per cent in days off from sickness for those taking the service,<sup>3</sup> as compared with 46 per cent in a large group elsewhere<sup>4</sup> when controls were complete.

### DISCUSSION

Because of the loss to industry caused by absenteeism, and because of the greater loss in lessened efficiency of the workers when on duty, it is only logical that definite steps should be taken to prevent sickness. The success of the physical-fitness service in accomplishing this purpose, wherever tried, has demonstrated its value.

The cost of the service is relatively small because the bulk of the work is done by a lay person, the trained physical-fitness worker. One such person, with the part-time aid of a physician and a secretary, is able to conduct the service for a group of from 1800 to 2000 persons and handle from 4000 to 5000 return visits a year.

Patients are willing to pay for medical service when they are sick but not for health service when they think they are well. Therefore, the expense must be borne by the employer. The employer is justified in assuming this expense because of resulting reduction in absenteeism, increased efficiency and improvement in morale.

To the cost of days off for sickness must be added the loss from lessened efficiency, for when health is impaired the higher powers are first affected — judgment, initiative, endurance and personality. This loss is most evident among the higher paid executives, on whose efficiency the success of the industry rests.

True health examinations, which are necessary for successful health work, are not now available because the usual so-called "health examination" is an examination for disease. Thus, to obtain its benefits, the subject must be sick before he can be well.

The physical-fitness clinic functions as a screening clinic not only to determine the causes of impaired health but also to identify disease and send such patients to their own physicians and dentists.

The number of physical defects and faulty health habits and the number of return visits of the female employees were in like proportion to those of the males.

The twenty-four-hour list of activities demonstrates the helplessness of the average person in planning his day to conform with the essentials of health. The fault lies not so much in working con-

ditions, in the improvement of which industry has made epochal advances, but chiefly in the time off from work — especially Saturdays and Sundays, which are usually periods of irregularity and of activities that make for dissipation of health reserves, rather than of recuperation. Hence, "Black Monday" is proverbial in industry.

By his return visits to the clinic, the applicant is encouraged and receives the fundamental health instruction necessary for him to obtain optimum results. During the period when he is working for better health by correcting his faulty health habits, he forms good health habits that continue throughout his working life, for good habits are as persistent as faulty ones.

The physical-fitness clinic, properly conducted, brings to the patient not only the resources of present-day medical knowledge but also the newer knowledge of factors contributed by allied science — especially those relating to the functions of the body as affected by irregularity, overfatigue, lack of sunlight and disturbed physiologic processes.

The diagnosis of health is a challenge to the best skill of the physician — as stated by Theobald Smith, "The diagnosis of health is more difficult than the diagnosis of any disease."

The desire for better health is universal, and the patient needs only to be convinced that habits are really faulty, and to receive definite directions for correcting them, to co-operate willingly. His success makes the atmosphere of the clinic a happy one both for himself and for the clinic workers — all striving for a common purpose.

### SUMMARY AND CONCLUSIONS

A physical-fitness service offered to approximately 900 executives and employees of the Blue Cross at their Boston home office is described.

The results obtained answered wholly or in part the following questions:

To what extent were they interested in working to improve their health?

Attendance at the clinic was voluntary except for 313 new employees who entered the organization with the understanding that they would be required to have the health examination and return once a year for a check-up, 422 of the remaining old employees applied for the examination — a total of 735.

Did they know they had health habits essentially faulty?

Only 5 applicants answered in the affirmative when asked, "Have you any health habits injurious to your health?" Thus 730 were unaware that they had such faulty health habits, although when checked 2294 were found.

When faulty health habits are identified, will they correct them?

In the six-month period, 2822 return visits were made by those working to correct them.

If they work to correct these habits, what results can they obtain?

Their improved health was the cause of the continued visits. A partially controlled group of 100 applicants showed a reduction of days off from sickness of 26 per cent, as compared to a reduction of 46 per cent in a similar group in which controls were complete.

Eighty-eight cases in the danger zone of overweight lost from 1 to 28 pounds, a total of 574 pounds. Eighty-eight cases in the danger zone of underweight gained from 1 to 15 pounds, a total of 247 pounds, and 14 patients with systolic pressures ranging from 150 to 210, were found, at the end of the period of return visits, to have reduced the systolic pressure an average of 20.

Of the 735 applicants examined, 110 had no physical defects aside from overweight and underweight. None were entirely free from faulty health habits.

Twenty-seven per cent were referred to their family physicians, and 17 per cent to their family dentists.

A check-up of their twenty-four-hour periods of activity showed that faulty health habits were oc-

casioned chiefly by conditions outside rather than during working hours.

The clinic demonstrated that both executives and employees need only to have their faulty habits identified and definite directions given for their correction to obtain efficient co-operation in working for better health.

I am indebted to Mr. R. F. Cahalane, executive director of the Blue Cross, for the invitation to conduct this clinic and to Mr. H. Proctor Redd, director of public relations, Mr. Harry Healy, director of personnel, and Dr. Charles G. Hayden, medical director, Blue Cross, for their cordial cooperation.

Personnel of the clinic included Albert C. England, M.D., examining physician; George M. Olive, Jr., M.D., and L. Murray Shipp, M.D., examining physicians; Helen M. Sanderson, physical fitness worker; and Martha Freedman, secretary and statistician.

290 Commonwealth Avenue

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## MEDIAL PTOSIS OF THE KIDNEY\*

### A New Renal Syndrome

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BOSTON

**P**ROBABLY on more than one occasion urologists have examined patients for pain or discomfort that, because of its character and location, was thought to be of renal origin, only to find the pyelographic studies normal. In at least a few of these cases the symptoms may be due to medial ptosis of the kidney.

Caudal mobility of the kidney with the body in the vertical or upright position (ptosis of the kidney) has been known for many years as a clinical entity, with alternate periods of popularity and disrepute. This paper is not directly concerned with that subject.

Little or no attention has been given to medial or lateral mobility of the kidney, and the pyelographic demonstration of an abnormal degree of medial mobility has not, to my knowledge, been previously described. "Medial ptosis of the kidney" has been chosen as a term to describe abnormal medial mobility of that organ. With a patient lying on the left side the condition of medial ptosis of the right kidney would be shown by abnormal change of the position of the right kidney toward or beyond the vertebral column. Similarly, medial ptosis of the left kidney might be demonstrated with a patient lying on the right side.

This condition, which may be the cause of symptoms, cannot be demonstrated by the usual pyelographic technique. The diagnosis can be made, however, by means of x-ray films using anteroposterior projection with the patient in the lateral position (Fig. 1). After cystoscopy and ureteral catheterization or during intravenous pyelography the patient is placed on a litter lying on his side, with the painful side up. The patient's back is placed firmly against an upright x-ray table used for gastrointestinal or chest x-ray examination, or against a cassette, 35 by 65 cm., in front of which has been placed a portable Sieman's microgrid. The x-ray tube is then focused for an anteroposterior view of the kidney region. A retrograde pyelogram is then made, with the ureteral catheter pulled down into the lower ureter before the x-ray film is taken. A routine film taken in this position during intravenous pyelography may be used instead.

To determine the normal extent of medial mobility of the right kidney with the patient lying on the left side, films were taken in the position shown in Figure 1 after pyelographic studies had been completed in a number of patients. As illustrated in Figures 2 and 3, these studies showed no medial descent of the kidney in the normal person.

\*Presented at a meeting of the American Association of Genito-Urinary Surgeons, June 5, 1947, Atlantic City, New Jersey.  
†Resident-in-charge for urology, Boston City Hospital.

‡Manufactured by the Libel Fl. & Co. Company, Cincinnati, Ohio.

The condition of medial ptosis has recently been demonstrated and corrected in 2 patients. Both

were slender women who had moderate pain and distress in the right upper quadrant of the abdomen

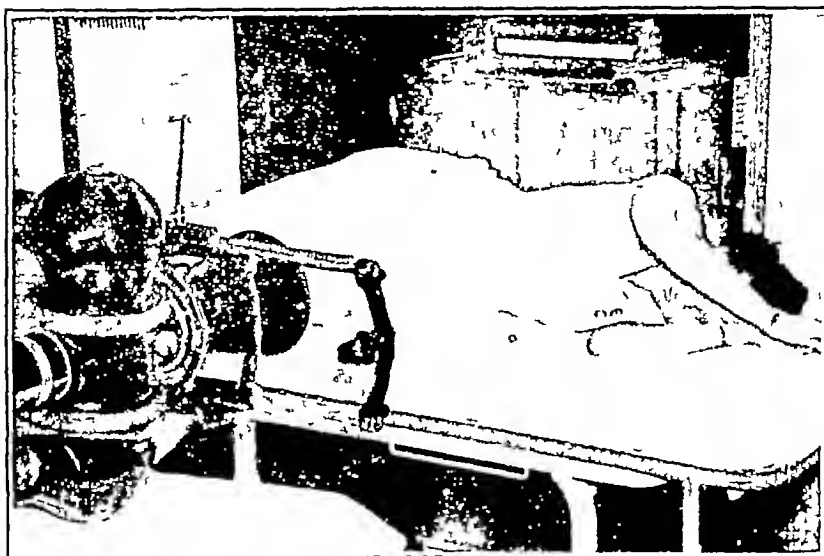


FIGURE 1 *Position of Patient for Pyelogram to Demonstrate Abnormal Medial Mobility of the Right Kidney*

*X-ray film taken as an anteroposterior projection, with the patient in the lateral position and with the painful kidney up*



A



B

FIGURE 2 *A Shows a Normal Pyelogram in the Supine Position, and B a Pyelogram of the Same Patient in the Position Shown in Figure 1 (The Right Kidney Remains in Normal Position)*

and the right flank. At times the symptoms were noticed or were aggravated when the patient was lying or sleeping on the left side. Physical activity also frequently produced discomfort. Mild gastrointestinal symptoms appeared to be associated with the pain. There were no urinary symptoms. Both patients had obtained relief by resting in a supine



position. Physical examination in each case was negative, except that a suspicion of an abnormally movable kidney was created by palpation of the upper portion of the abdomen with the patient lying on the left side, and in 1 case the kidney could be felt in the epigastrium while the patient was in a similar position. X-ray studies of the gall bladder,



FIGURE 3 A Shows a Normal Pyelogram in the Supine Position and B a Pyelogram of the Patient in the Position Shown in Figure 1 (The Right Kidney Remains in Normal Position. Note Fluid Level in Kidney)



FIGURE 4 A Shows a Pyelogram of Patient A in the Supine Position and B a Pyelogram of Patient B in the Supine Position



stomach and intestines were reported as negative. Intravenous urograms were likewise normal. The

the extent of caudal mobility with the patients in an upright position — patient "A" shows some,

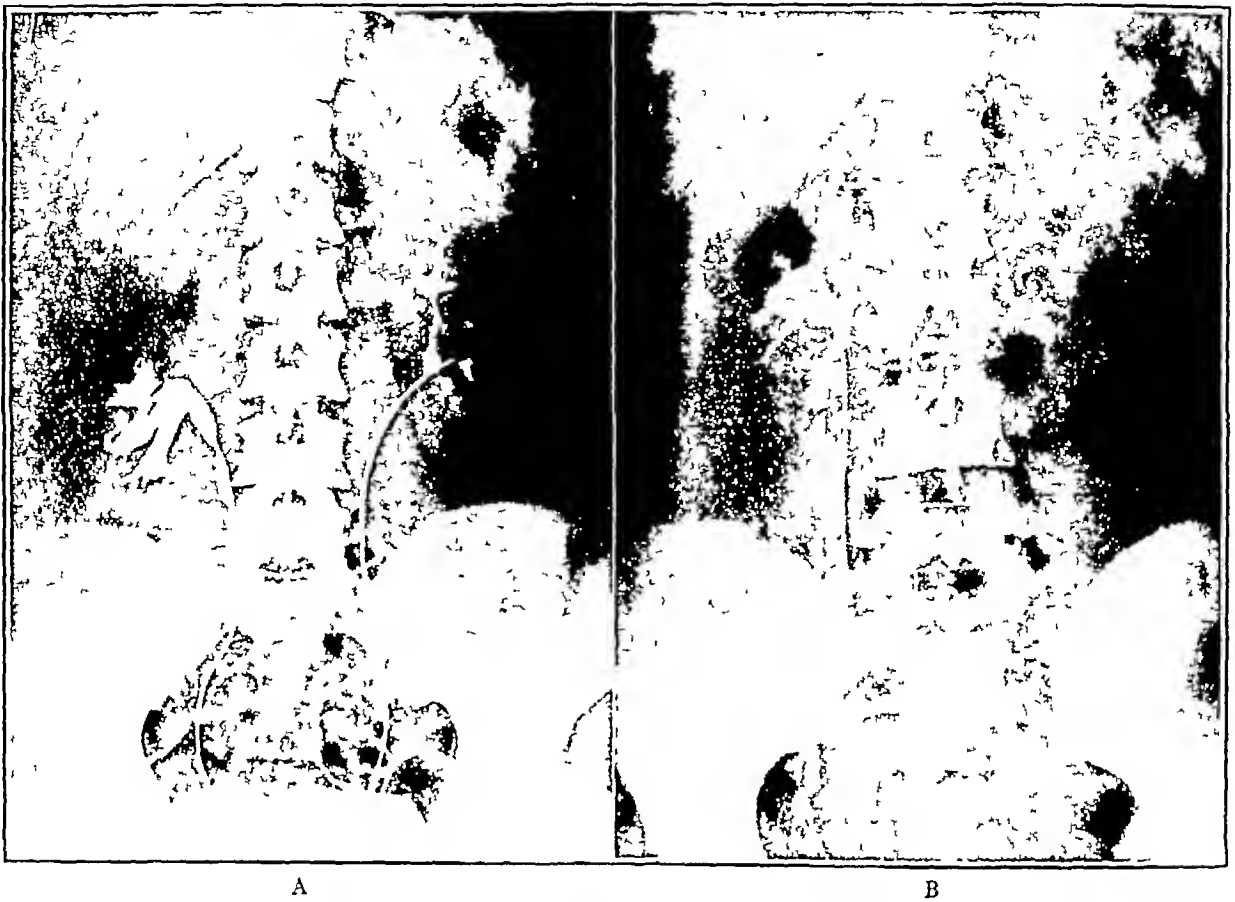


FIGURE 5 A Shows a Pyelogram of Patient "A" in the Upright Position, and B a Pyelogram of Patient "B" in the Upright Position

question of medial ptosis arose, and special studies of the right kidney established the diagnosis

but not significant, vertical ptosis, whereas patient "B" shows none. From these films it certainly

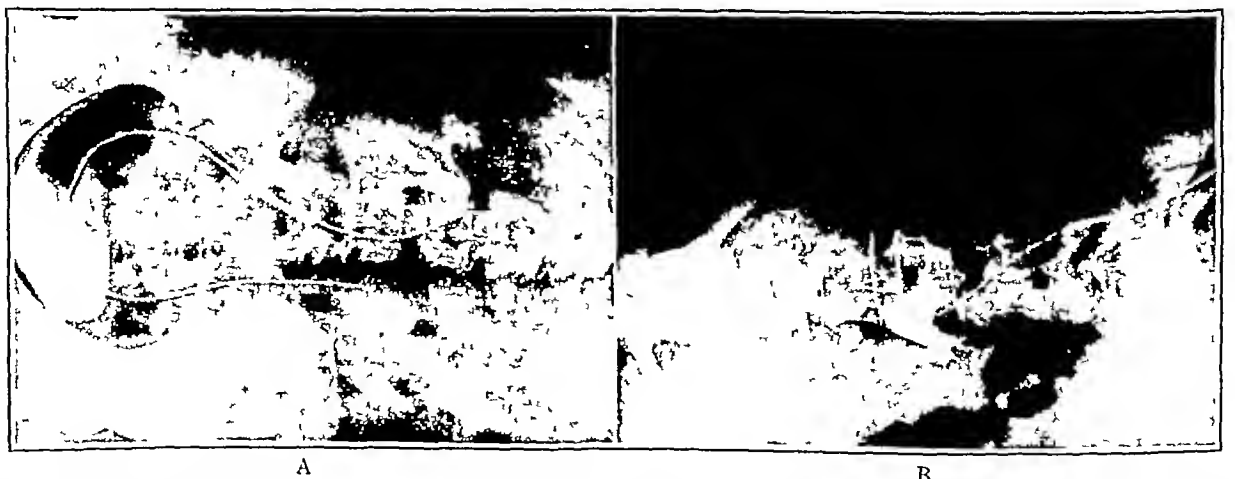


FIGURE 6 A Shows a Pyelogram of Patient "A" in the Position Shown in Figure 1 — There Is Abnormal Medial Mobility of the Kidney in This Position, B Demonstrates a Pyelogram of Patient "B" in the Position Shown in Figure 1 — There Is Abnormal Medial Mobility of the Kidney, Which Has Dropped Beyond the Midline and Carried the Ureter with It

Figure 4 shows the retrograde pyelograms in the supine position in each patient. Figure 5 reveals

would not be possible to state that the right kidney was the cause of symptoms in either case.

However, by means of films taken in the position described above (Fig 6) a significant degree of medial ptosis had been corrected in each case

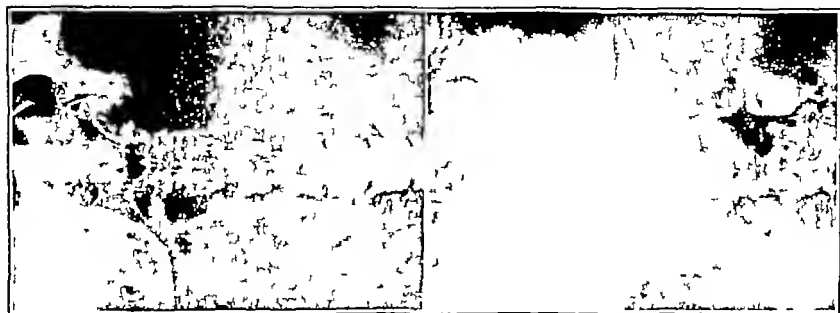


FIGURE 7 A Shows a Postoperative Pyelogram of Patient L in the New Position (Kidney Is Now in Normal Position) B Demonstrates by Postoperative Pyelogram of Patient L in the New Position with the Kidney in Normal Position (The Fluid Level in the Kidney and the Fetal Spine Can Be Seen)

medial ptosis of the right kidney could be demonstrated in both patients, patient "B" appeared to have a considerable degree of medial mobility.

Nephropexy was performed on both patients with complete relief of symptoms and postoperative

It is my belief that this syndrome may explain some of the hitherto undiagnosed symptoms referable to the kidney regions and the upper abdominal quadrants. Nephropexy is a simple method of correcting the condition.

## A DEVICE FOR CONTROLLED NEGATIVE PRESSURE

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BOSTON

**T**HIS article presents a simple compact device for the safe administration of controlled negative pressure to the gastrointestinal tract of patients in institutions having built-in negative-pressure systems

Some of the difficulties and inconveniences previously encountered in the use of suction apparatus

inflow and outflow tubes attached — an arrangement that allows the tops to be easily removed for emptying the bottles and to be easily replaced and made airtight. The bottles fit in a stainless-steel rack, which hangs from the frame of the hospital bed (Fig 1). Thus, the rubber tubing is kept at a minimum, and the device is off the floor and out of the way when the bed is being made or moved.

The overflow bottle (Fig 2) rarely needs opening except when the drainage bottle has been allowed

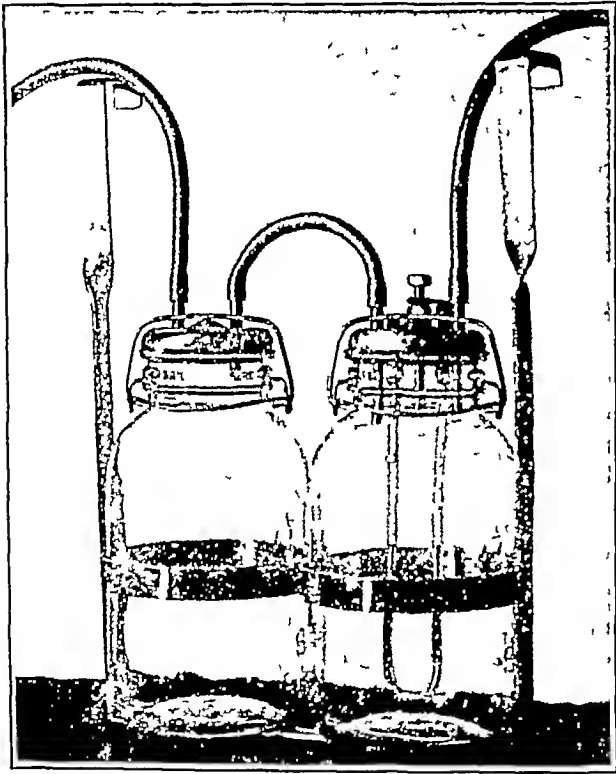


FIGURE 1 Photograph of the Device in Its Stainless-Steel Rack. This rack was designed and constructed by Mr. Edward Hallinan.

prompted the development of this device. Any apparatus, when on the floor, is likely to be tipped over or broken and makes cleaning of the room difficult. Bulky glass apparatus, if strapped on the bed frame, is likewise often broken. Many rubber tubes leading to and from the apparatus are often draped over the bed and the patient. Glass connectors in rubber-stoppered bottles are easily shattered, and may injure the hands of the attendants.

This device consists of two 2-liter "Atlas" preserve jars, one for drainage and the other for overflow. The bottles are fitted with cast-brass duplicates of the original snap-on glass tops, with brass

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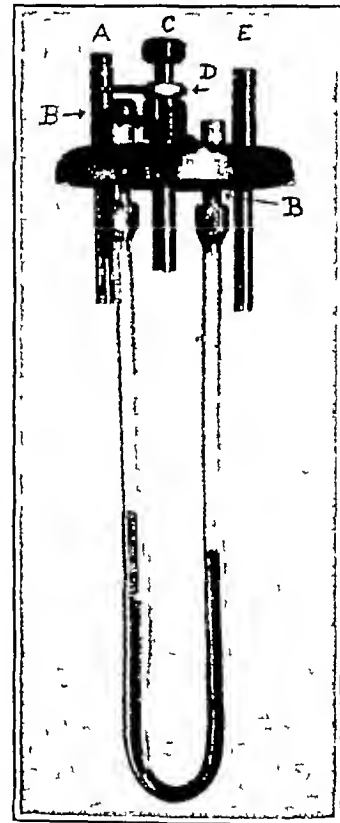


FIGURE 2 Photograph of the Top of the Overflow Bottle, with Its Attachments.

A shows flow-control unit in outflow tube, B leather-covered manometer opening, C adjustment bolt for negative-pressure release valve, D lock nut, and E inflow tube.

to overflow into it. Should the overflow bottle become full, the downward extension of the outflow tube will not permit the fluid level to reach any vulnerable part. The overflow bottle has three special features. The first, a flow-control unit attached to the outflow tube, is a bolt that has been drilled with a small-caliber drill. The resulting small orifice per-

mits the wall valve to be fully opened, since it automatically allows only a small volume of air to flow through the device per unit of time. Careful flow adjustments at the wall valve are therefore unnecessary. The second feature is a mercury manometer incorporated in the device, which accurately shows the observer at a glance the degree of negative pressure in the system. The ends of this manometer are leather covered. One end opens inside, and the other outside the bottle. This arrangement permits no mercury to escape and yet allows sufficient air flow for the manometer to function. The manometer tube is made of "Tenite II," an Eastman Corporation clear thermoplastic that is difficult to break. The connectors must be made of a metal such as aluminum or stainless steel that will not amalgamate with the mercury. The third feature, a negative-pressure release valve, is also incorporated in the device, with a range of adjustment from 0 to 6 inches of mercury — 3 inches of mercury is roughly equivalent to 40 inches of water, which is the usual working range for gastrointestinal suction. The negative pressure release valve is a ball valve with adjustable spring tension. A metal ball sits on top of a spring in the hollow valve housing, and the valve seat is at the base of the hollow adjustment bolt, to which a lock nut is attached. The air intake is beneath the head of the adjustment bolt so that it cannot be inadvertently occluded.

By means of the features mentioned above a system is set up that causes a constant stream of air to flow through the overflow bottle, entering via the air intake and leaving by way of the small orifice in the flow-control unit. The negative pressure in the overflow bottle is variable, being changed by increasing or decreasing the spring tension, which forces the metal ball against the valve seat (Fig. 3). The negative pressure is registered on the manometer and transferred through the drainage bottle to the patient. Variations in the negative pressure in the main hospital system do not affect the negative pressure in this device, provided the negative pres-

sure in the hospital system does not fall below that in the device.

#### SUMMARY

A device for safely administering controlled negative pressure to the gastrointestinal tract of pa-

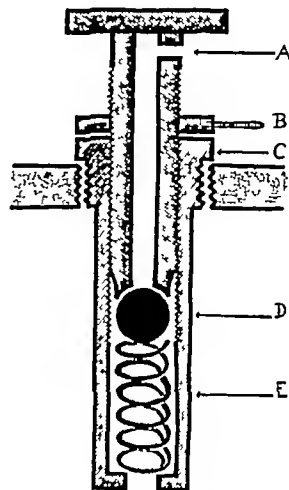


FIGURE 3 Diagram of the Negative Pressure Release Valve. A demonstrates air intake beneath the head of the adjustment bolt. B lock nut with attached handle for tightening and releasing. C hollow valve housing. D metal ball and E, spring forcing metal ball against the valve seat.

ients is presented. The apparatus is simple in design, and the parts are inexpensive. Its breakable parts are its cheapest and are readily obtainable. It has proved simple to operate for members of the nursing staff who have used it.

## MEDICAL PROGRESS

### THE "NEPHROTIC SYNDROME" (Concluded)\*

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#### HYPOPROTEINEMIA

The return of the plasma protein concentration toward normal as the urinary protein loss decreases indicates clearly that proteinuria is most important in the pathogenesis of hypoproteinemia. However, there is reason to believe that other factors are concerned in this phenomenon. On occasion the daily protein loss may exceed 30 gm, but usually it lies between 5 and 10 gm.<sup>74, 75</sup> This appears to be relatively small in terms of protein replacement capacity. Co Tu<sup>76</sup> estimates, on the basis of changes observed in animals after plasmapheresis and in human blood donors after repeated blood letting, that normal man should be capable of manufacturing approximately 55 gm of protein per day, provided an adequate diet is given. Some patients with the nephrotic syndrome can maintain a constant (though low) plasma protein concentration by manufacturing at least 20 gm of protein per day to replace that lost in the urine. But others fail to replace even this much, and it may be posited that there is a fundamental impairment of protein synthesis in the nephrotic syndrome that varies quantitatively from case to case.

The evidence regarding this point is confusing, fragmentary and often contradictory. Very few patients can be or have been subjected to the necessary expensive and protracted balance studies. It is very difficult to be sure that the data of different studies are comparable. But it now seems certain that increasing the dietary protein intake does not usually result in augmented plasma protein synthesis. Berglund, Scriver and Medes<sup>77</sup> and others<sup>78</sup> have found that the plasma proteins increase slightly in response to high-protein feeding and that proteinuria may be remarkably exaggerated. Farr<sup>79, 80</sup> and others,<sup>81</sup> on the other hand, failed to find any change.

Similarly, disagreement is evident regarding basic nitrogen needs. In children it appears to be very difficult to maintain a positive nitrogen balance.<sup>79, 80</sup> The optimal intake is not much in excess of the needs of a child of the same age and ideal weight, and only slightly greater protein intake may have a toxic effect by reducing protein assimilation.<sup>82</sup> Ad-

ministration of amino acids, by mouth or, better still, by vein, seems to counteract this effect to some extent.<sup>83</sup> In most adults nitrogen equilibrium is more easily achieved, although utilization of protein is determined by the caloric intake and by the character of the protein and amino acid mixture ingested. The divergencies between nitrogen needs for children and adults may be in part attributable to the factor of growth and, when this is of no importance, to differences in the extent of protein depletion.

The plasma proteins are believed by many workers to be in equilibrium with an extensive "protein pool" the bulk of which is extravascular.<sup>84</sup> Reduction of the plasma protein accordingly denotes reduction of the total labile body protein, and repair of a plasma protein deficit entails replacement throughout the pool as a whole. Very little is known of the measures employed by the body to protect the composition and size of the pool, though it appears that a fall in plasma protein stimulates manufacture and possibly reduces catabolism. Moreover, catabolism is lowered during starvation to a minimum commensurate with intracellular activity and caloric needs.<sup>85</sup> When an adequate caloric intake is assured and only nitrogen withheld, a still greater reduction occurs, though it appears that some 20 gm of protein is destroyed even then each day. It is not known how protein degradation and nitrogen excretion are reduced in starvation, but the same processes are probably operative in the nephrotic patient, since, almost without exception, such patients lose tissue protein and present striking emaciation after removal of edema fluid therapeutically or by spontaneous remission. In experimental animals plasmapheresis has also been found to draw upon proteins essential in hemoglobin production.<sup>86</sup> Perhaps this explains the anemia seen in some cases of nephrosis. Hence, it seems reasonable to regard the nephrotic syndrome as a state of quasistarvation in which nitrogen requirement is reduced to a minimum. Nonetheless, the nephrotic patient has a nitrogen requirement considerably in excess of the sum of the theoretical minimum and the amount of nitrogen lost in the urine, possibly to meet the need of replenishing a depleted protein pool or to replace tissue protein.

It is not quite clear why the protein pool should be depleted. Certainly, many patients continue to have excellent appetites and to consume consider-

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able amounts of protein food throughout the course of their illness. It must be assumed that very large quantities of protein are lost in the urine when the plasma protein level is still normal, before symptomatology demands the attention of the physician. Patients may be expected to differ markedly in the extent to which this process has been carried. Thus, in Berglund's<sup>17</sup> series a lag period of several days following the administration of a high-protein diet intervened before increased plasma protein synthesis became evident in a slight increase in plasma protein concentration and proteinuria. This period may represent the time required for the restocking of the extravascular component of the protein pool. In contrast, in only 1 patient studied by Keutman and Bassett<sup>11</sup> did the plasma protein level rise and then only because proteinuria slacked off. Hence depletion may have been more marked in their patients. It is possible, of course, that these observations indicate the inadequacy of the protein pool concept in this connection, since nitrogen may be required for the building of stable proteins as well as labile components of the pool.

Theoretically, the ideal replacement material should be concentrated purified fractions of the human plasma proteins, but unfortunately these substances have often failed to increase protein concentration satisfactorily.<sup>17-19</sup> Nor is there any evidence that protein synthesis is stimulated by the additional protein intake. One difficulty arises from the fact that the injected protein is immediately distributed throughout the protein pool. Luetscher<sup>27</sup> has found that a small percentage of injected albumin appears in the urine, that most of the remainder disappears from the blood within forty hours and that only a small fraction remains in the circulation. When one considers the probable size of the protein pool this behavior is not unexpected. In the starved dog the ratio between extravascular and intravascular protein is 25:1, indicating that a total increment of 25 gm. of protein is required to increase plasma proteins by only 1 gm.<sup>28</sup> If this ratio were 10 in nephrotic patients, it is evident that 300 gm. of plasma protein must be given to increase the plasma protein concentration by 1 gm. per 100 cc. Even when adequate protein is furnished, however, repletion appears impossible in many patients. Moreover, it cannot be explained why endogenous protein synthesis should not be sufficiently effective to make more than 5 to 10 gm. of plasma protein daily in excess of metabolic needs when adequate dietary protein and a high intravenous protein intake are assured.

More direct evidence that a disturbance of nitrogen metabolism occurs is found in the behavior of the amino acid level in certain cases. Farr and MacFadyen<sup>29</sup> have observed a chronic reduction in the plasma amino acid concentration (ninhydrin method), which is accentuated prior to and during the "nephrotic crisis" in children with the nephrotic

syndrome. These episodes are characterized clinically by fever and abdominal pain occurring in association with a peritonitis for which, in many cases, there is no demonstrable infectious cause. Administration of amino acids parenterally is believed to have reduced the mortality of crisis.<sup>30</sup> Farr<sup>29</sup> thinks that the low level of amino acids may betoken "toxic destruction" of proteins since it is associated with a negative nitrogen balance and excessive nitrogen urinary loss. A similar hypoaminoacidemia has been observed in normal persons<sup>31</sup> during various infectious diseases and after trauma or operation. It is interesting that in these situations it is also attended by nitrogen loss and evidence of "toxic" proteinolysis. These phenomena cannot be explained at present, but it is possible that the patient with the nephrotic syndrome suffers continuously a similar defect in nitrogen metabolism that interferes with protein production.

It is of interest that dietary protein restriction coupled with plasmapheresis in dogs results in a marked hypoproteinemia characterized like the nephrotic syndrome by a marked decrease in the albumin fraction.<sup>32</sup> The maintenance of the plasma globulin concentration despite equivalent loss probably indicates more efficient replacement. It seems not unlikely that the failure of plasma globulin to fall in nephrosis in the presence of a depleted protein pool may likewise imply continued normal globulin synthesis and whatever defect there may be must concern albumin synthesis directly.

The principal site of albumin manufacture is believed to be the liver.<sup>33</sup> Few studies of liver function have been made during the nephrotic syndrome. Lytle et al.<sup>34</sup> found that nephrotic patients removed injected amino acids from the blood as readily as normal persons, whereas children with liver disease failed to do so. Moreover, Kirk<sup>35</sup> has shown that deamination of glycine proceeds normally in this disease. Galactose and bromsulphalein removal have been observed to be normal or occasionally only slightly impaired in other patients.<sup>36</sup> It is possible that these discrete activities are undisturbed even though hepatic protein synthesis is seriously deranged.

Since nephrotic patients appear to secrete little sulfur relative to nitrogen, it has been suggested that "deposit" protein<sup>37</sup> — characterized by a low sulfur content, presumably in the intracellular compartment of the protein pool — is chiefly concerned in urinary protein loss. Grabfield<sup>38</sup> considers a defect in the intermediary sulfur metabolism to be essential to the pathogenesis of the nephrotic syndrome. However, his work is based upon the total nitrogen and sulfur content of the urine. Hence it is possible that excessive excretion of nonprotein nitrogen is the cause for the observed reduction in nitrogen-sulfur ratio rather than a truly low nitrogen-sulfur ratio of urinary protein. Studies of nitrogen and sulfur metabolism with radioactive tracers

in the nephrotic syndrome are awaited with great interest

Epstein<sup>97</sup> has called attention to the possibility that a disorder of thyroid activity is involved, since the basal metabolic rate is frequently reduced. It is now generally believed, however, that this finding is of questionable significance. Edema<sup>98</sup> and the state of quasistarvation<sup>85</sup> may suffice to reduce the basal metabolism. Treatment with thyroid extract and thyroxin has proved disappointing.<sup>14, 85, 99</sup>

Insufficient evidence is at hand to prove conclusively that a faulty protein metabolism, particularly in plasma albumin synthesis, is in part responsible for hypoproteinemia. The irregularity of protein production and excretion in different patients, the failure to replace protein despite adequate and proper nitrogen supply and the signs of "toxic" protein destruction, including hypoaminoacidemia and negative nitrogen balance, seem to indicate this possibility. Nonetheless, protein loss in the urine is probably of the greatest importance since it appears to be essential to the development and maintenance of a low concentration of protein in the blood.

### EDEMA

From the standpoint of the patient, edema is the most distressing and disabling manifestation of the nephrotic syndrome. The distribution of subcutaneous fluid appears to be governed by gravity and tissue tension. Burch<sup>100, 101</sup> has shown that the predilection for the eyelids (particularly the lower lid) may be attributed to the low tissue pressure and the high distensibility of the skin in this area. Failure of lymphatic drainage when the eyelids are motionless and not blinking, as during sleep and during recumbency, explain the tendency for edema fluid to accumulate about the eyelids during the night. The genitalia and loose abdominal wall of many multiparas present similar characteristics and are often excessively edematous. This fluid may be under considerable pressure since the skin over the lower extremities may become shiny white and quite taut, often cracking and splitting under the strain. Edema fluid drains profusely through such breaks in the skin, and secondary infection, especially dangerous in these patients, may follow. Great discomfort may result from the restriction of movement. Pleural effusion or ascites often reduces the vital capacity greatly, and acute pulmonary edema occasionally appears. Localized edema of the glottis may prove rapidly fatal. Edema of the gastrointestinal tract<sup>102</sup> may account for radiologic evidence of delayed gastric emptying time and decreased motility of the small intestine.

The pathogenesis of nephrotic edema is not yet settled. Many discussions of this question fail to consider it in its entirety. Importance is attached, on the one hand, to the plasma protein concentration in relation to the osmotic pressure acting across

capillary membranes throughout the body as a determinant of the volume of interstitial fluid and, on the other, to renal activity in excreting or retaining water and electrolytes. Obviously, both factors are interrelated and interdependent. Neither should be stressed unduly to the exclusion of the other.

There is little doubt that a lowered plasma protein concentration results in the formation of edema.<sup>17, 103, 104</sup> Leiter<sup>105</sup> and others<sup>106, 107</sup> have proved conclusively that the removal of plasma proteins and low-protein diets lead to persistent hypoproteinemia and the development of edema in experimental animals. Starling's<sup>108</sup> hypothesis that the distribution of extracellular fluid is dictated by balanced transcapillary pressures — plasma oncotic pressure and tissue tension opposed to interstitial fluid oncotic pressure and capillary blood pressure — has been applied in explaining this phenomenon, in particular by Epstein,<sup>6</sup> who is largely responsible for the following viewpoint. Other things being equal, a reduction in plasma protein concentration connotes reduction in plasma oncotic pressure. This is even more likely in the nephrotic syndrome, in which the proteins of greatest osmotic activity are specifically withdrawn from the blood.<sup>109</sup> Moreover, many measurements of plasma osmotic pressure<sup>110-112</sup> reveal far greater diminution in the nephrotic patient than can be accounted for on the basis of the technical errors of the relatively crude methods thus far employed. Hence it may be presumed that the fall in oncotic pressure leads to increased filtration of water and diffusible solutes into the interstitial spaces, with an expansion of extracellular extravascular water volume and the formation of edema. The factors concerned in effecting a new equilibrium of the transcapillary forces are not easily discerned. Possibly, filtration in excess of reabsorption continues until an increment in tissue tension corrects the deficit in oncotic pressure.

According to this hypothesis the movement of fluid into the tissue spaces must occur at the expense of the plasma volume. The published figures for plasma volumes are conflicting.<sup>113-117</sup> In part, this may be attributed to errors introduced by lipidemia in various dye-dilution technics.<sup>37</sup> And in part it appears to be a result of a true variability in plasma volume. In accord with theory, plasma volume appears to be reduced in most cases. The most reliable studies, based upon measurements with carbon monoxide, indicate that the reduction of plasma volume is much less when anemia is a complicating factor. With diuresis, the plasma volume rises above normal in such cases, accounting, perhaps, for divergent observations.

Epstein's hypothesis is weakened considerably by observations that diuresis and loss of edema may occur in the absence of any detectable change in plasma protein concentration.<sup>118</sup> Plasma osmotic pressure may even fall. Similarly, in hunger edema, which resembles nephrotic edema in many respects,

the extracellular water volume may expand or contract without reference to protein concentration,<sup>119</sup> though it is claimed that osmotic-pressure changes are of chief importance.<sup>120</sup> Here, again, attention has been focused upon possible changes in the peripheral circulation. Keys<sup>119</sup> suggests that the capillary wall is in a state of 'dynamic non-equilibrium,' an assertion that is somewhat difficult to understand. Increased capillary permeability would increase effective filtration pressure across capillary walls and lead to edema formation. However, evidence that this occurs is unsatisfactory. The edema fluid and transudates contain very little protein, usually less than 0.5 per cent.<sup>121</sup> On the other hand, Luetscher<sup>87</sup> has found that injected albumin rapidly disappears from the blood, and Lange and his co-workers<sup>122</sup> claim that fluorescein bound to protein passes easily into the edema fluid. These observations require critical testing before they can be accurately evaluated. A third of the osmotic activity of plasma proteins depends upon their electrical charge and the resulting unequal distribution of diffusible ions on each side of the capillary membrane (the Donnan equilibrium).<sup>123</sup> A change in this characteristic, thus far not detected, may be a factor in determining equilibrium conditions in the capillaries and the distribution of extracellular water. Perhaps alterations in the capillary wall are influential in affecting this factor. Changes in over-all tissue tension and capillary pressure cannot be appraised with accuracy by the methods at present available.

Moreover, the use of albumin concentrates to repair the deficit in plasma albumin has proved rather disappointing.<sup>124, 125, 126</sup> Diuresis and mobilization of edema may occur in some cases, but the effect is often limited and unimportant. Marked increases in plasma volume may prove detrimental and prevent theoretically appropriate therapy, a development that would not be expected if reduced protein concentration were the sole important defect.

Opposed to the view that changes in the blood or at the periphery have primacy in determining the volume of extravascular fluid is the belief that renal dysfunction in the disposal of water and electrolytes is chiefly concerned. Certainly retention of water by the kidneys is required and does occur. One school of thought posits a specific fault in renal excretion of sodium.<sup>127, 128, 129</sup> This claim is now supported by a considerable body of evidence, but it has been clearly proved that the nephrotic patient handles sodium in a manner that differs quantitatively rather than qualitatively from the normal.<sup>130</sup> Indeed, the normal kidney, in the face of a water and sodium deficit, acts like the nephrotic kidney. Hence the nephrotic patient appears to be in a state of quasis dehydration, which might be explained by diversion of water and electrolytes from the plasma into the interstitium. In addition, there

are disturbances of renal function that may contribute positively. The glomerulotubular imbalance, described above, might be expected to predispose to retention by enhancing water and salt reabsorption in excess of the body need. Diuresis, either spontaneous or induced by intravenous injection of salt-poor human plasma albumin concentrates, has been observed to occur in association with an increase in glomerular filtration rate.<sup>38, 87, 131, 132</sup> The resulting reversal of the imbalance should be important in the explanation of the increased output of urine. The possibility that increased formation of antidiuretic hormone by the posterior pituitary is responsible in part for the water retention has been suggested by the appearance of antidiuretic substances in the urine.<sup>127</sup> There is no evidence that the increased tubular reabsorption of sodium is a result of adrenal cortical dysfunction.

The alleviation of the nephrotic syndrome during various infectious diseases has frequently been observed.<sup>129-130</sup> Clement<sup>125</sup> has described regression of edema in response to the pyrogenic reaction following administration of typhoid vaccine, and deliberate infection with measles has been suggested as one means of treating the disorder.<sup>129</sup> Unfortunately, the effect of fever cannot always be predicted. In many patients, it proves definitely detrimental, inducing hematuria and further accumulation of edema. Moreover, patients with the nephrotic syndrome are peculiarly lacking in resistance, usually dying as the result of some intercurrent infection. Hence, the pyrogenic reaction must be condemned as a therapy, but it is of great interest in connection with the problem of the pathogenesis of nephrotic edema. Fever gives rise to striking changes in the renal and peripheral circulations. The cardiac output rises, and blood flow through the kidney and skin increases, apparently as a result of vasodilation. How these changes are related to the withdrawal of tissue fluid and diuresis is unknown, but they indicate that hemodynamic factors play an important role.

It is evident that knowledge of nephrotic edema is fragmentary. Many unassailable facts are at hand, but they cannot be fitted as yet into any satisfactory theory. Probably several variables are involved. The accumulation of fluid in the tissue spaces undoubtedly denotes an imbalance of transcapillary pressures and simultaneous water and electrolyte retention by the kidney. Mobilization of edema requires an adjustment in the periphery to promote the flow of fluid into the blood and a change in renal function to permit its excretion. Unilateral activity thus appears unlikely, but the fundamental activities in the peripheral vascular bed and the kidney are obscure.

#### LIPIDEMIA

One of the most puzzling manifestations of the nephrotic syndrome is the disturbance of fat



metabolism that gives rise to hypercholesterolemia and hyperlipemia. The elevated concentration of fatty materials may render the plasma opaque and milky in appearance, and greasy in consistence. There is a tendency for the fat to separate slightly on standing, and part of it may be removed by centrifugation, but a considerable quantity appears to be loosely attached to protein or to serve as a coating of protein aggregates,<sup>63, 131</sup> so that complete physical separation may be impossible by ordinary means. Cholesterol is a relatively insoluble substance, and yet 1 or 2 gm may be carried in solution in each 100 mm of nephrotic plasma. Such quantities cannot be dissolved in normal plasma, but even larger amounts can be held in solution in the nephrotic plasma.<sup>132</sup>

No clinical abnormality can be definitely ascribed to lipidemia. Certainly, atherosclerosis occurs more frequently among nephrotic patients than in normal persons of the same age.<sup>133</sup> It is in children with this disorder that one sees the most advanced forms of childhood arteriosclerosis. There appears to be a relatively constant coincidental, but by no means obligatory, relation to hypoproteinemia and edema. When edema clears, the plasma lipids tend to return to normal levels, and if edema continues to be evident, lipidemia may persist even though uremia develops.<sup>134</sup>

Plasma cholesterol is always elevated. Levels as high as 2.0 and 2.3 gm per 100 cc have been observed. All the other lipid fractions are likewise increased. Cholesterol esters appear to rise in most patients to the same extent as free cholesterol.<sup>86</sup> Peters and Man<sup>135</sup> found that the phospholipids (lecithin, the cephalins and other phosphorus-containing lipids) parallel cholesterol, whereas Thomas<sup>136</sup> observed a somewhat closer relation between lipid phosphorus and the total lipid content of the plasma. The neutral fats are always increased, and it has been observed that they tend to make up a larger fraction (as much as half) of the total lipids as the disease advances.

The fat content of the diet appears to have little influence upon the plasma composition. Hiller et al<sup>137</sup> and others<sup>138</sup> observed slightly greater increments in the plasma fatty acid and lecithin content after fat ingestion than in normal subjects or nephritic patients, but it appears that nephrotic patients can burn fats as efficiently as normal persons, since the respiratory quotient decreases in a normal manner when fat makes up the greater portion of the caloric intake.

The causes of lipidemia in nephrosis are quite obscure. In large part this is a result of the confused state of knowledge regarding normal fat metabolism. Since nephrotic patients appear to absorb and utilize dietary fat in a normal manner it has been suggested that lipidemia represents a failure of the processes of fat removal from the blood into storage sites.<sup>137</sup> Contrariwise, Thannhauser<sup>139</sup> claims that

lipidemia is due to enhanced mobilization of fat from the body stores. There is no evidence in support of either hypothesis. Since wasting of the tissues is prominent, lipidemia has been likened to that occurring in starvation, but in chronic malnutrition the cholesterol content of the plasma is usually depressed.<sup>85</sup> The possibility that a disorder of the thyroid gland is involved has likewise been considered<sup>140</sup> and found wanting, since there is no response to specific therapy and reductions in the basal metabolic rate may be apparent rather than real owing to a failure to use "ideal" body weights in calculations.<sup>141</sup> Heymann and Clark<sup>142</sup> and Winkler and his co-workers<sup>143</sup> have induced lipidemia in animals by bilateral nephrectomy and ligation of the ureters. Lipidemia also develops after nephrotoxic nephritis<sup>144</sup> and subtotal nephrectomy.<sup>145</sup> The cause of this phenomenon is unknown, but it does not seem to have any relation to the problem in nephrosis, in which renal function is usually relatively unimpaired. It appears that lipidemia must be considered a phenomenon connected in some way as yet unknown with the hypoproteinemia and edema of the nephrotic syndrome. Little light has been thrown upon this question by the experimental production of hypoproteinemia in animals. In this situation the development of lipidemia is apparently attributable to hepatic insufficiency,<sup>146</sup> but in the nephrotic syndrome, hepatic function appears to be normal.

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As a rule the nephrotic syndrome is distinctive, presenting each of the specific disorders discussed at length above. It should be emphasized, however, that it may be complicated by other independent disturbances, such as congestive heart failure, uremia and hypertensive heart disease. Extraneous manifestations that mask or distort the usual clinical and physiologic pattern may thus be introduced. Finally, the syndrome itself presents a shifting and variable course. The most striking clinical phenomenon, edema, may be minimal and even absent from time to time. Proteinuria, hypoproteinemia and lipidemia are fundamental derangements, and so long as they persist the nephrotic syndrome may be considered to be present. This concept is important in the interpretation of therapeutic effects, since transient elimination of edema cannot be considered as evidence for the curative power of any agent.

Another confusing aspect of the nephrotic syndrome is the diversity of its causes. The typical complex of symptoms and signs may develop during syphilis and clear completely in response to antibiotic or arsenical therapy. Chronic diffuse glomerulonephritis, intercapillary glomerulosclerosis, amyloid disease and other disorders give rise to the same clinical picture. Each of these may be distinguished only by the characteristic renal lesion

or clinical course, or both. In only one disorder, lipid, "genuine" or chronic nephrosis, is there no anatomic change in the kidney. Since even in this condition proteinuria and other manifestations appear to depend upon an abnormality of glomerular membranes, lipid nephrosis may also be primarily a renal disease.

In any case, the nephrotic syndrome can be profitably viewed as a discrete entity. As such it remains an unsolved riddle. Secondary infection, which was formerly devastating in these patients, can now be combated with powerful chemotherapeutic agents, but specific therapy is altogether lacking. It can only be hoped that the use of newer methods of study in the clarification of the metabolic, hemodynamic and renal function disturbances, of which the available evidence is indicative rather than demonstrable, may yield a clue to the means of effective treatment.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34081

#### PRESENTATION OF CASE

A forty-nine-year-old man entered the hospital because of difficulty in urination.

For two months he had frequency (ten times during the day and five times at night). This was associated with weakness and hesitancy of the stream. There was no dysuria, gross hematuria, back pain, feverishness or vomiting. One week before entry he had an attack of dyspnea, wheezing and cough, and he developed conjunctival and palpebral hemorrhages. The blood pressure was 120 systolic, 80 diastolic. The legs became edematous.

Physical examination revealed a pale drowsy man. The face was puffy, and there were conjunctival and palpebral hemorrhages. The eye grounds revealed flame-shaped hemorrhages, narrow arteries and blurring of the disk margins. The neck veins were distended and pulsating. There was an apical systolic murmur. In the abdomen there was a fluid-filled, tense, nontender mass extending upward from the pelvis to the level of the umbilicus. Rectal examination revealed tender external hemorrhoids and a questionably enlarged prostate. The legs and feet were edematous.

The temperature was 99°F, the pulse 88, and the respirations 16. The blood pressure was 175 systolic, 90 diastolic.

Examination of the blood disclosed a hemoglobin of 5 gm and a white-cell count of 7300. The non-

protein nitrogen was 200 mg, the calcium 6.8 mg and the phosphorus 8.2 mg per 100 cc, the alkaline phosphatase was 30 units, and the carbon dioxide was 10.6 milliequiv per liter. The prothrombin time was 18 seconds (control, 17 seconds). Repeated examinations of the urine gave a reaction of pH 6.0 to 7.0, with a specific gravity of 1.008 to 1.014, and a + to ++++ test for albumin. The sediment showed many red cells and on one occasion 20 to 30 white cells per high-power field. Cultures grew colonies of *Staphylococcus aureus* and colon bacilli.

An electrocardiogram showed digitalis effect only. An x-ray film of the chest revealed basal congestion of the lungs and some left ventricular hypertrophy. A plain film of the abdomen was normal.

The patient was catheterized in the Emergency Ward, and 750 cc of clear urine was removed. A few hours later, after several unsuccessful attempts to pass a No. 18 catheter, a No. 20 Foley catheter was passed without difficulty, and 1000 cc of clear urine removed. There was a good deal of subsequent bleeding into the bladder, and clots were removed by irrigations as required. He was digitalized and given resuspended red cells in 10 per cent dextrose in water. Fluids were forced to 4000 cc a day. The palpebral hemorrhage and edema gradually subsided. After a few days the indwelling catheter became very painful. He began to vomit, and fluids were then pushed intravenously and by proctoclysis. The uremia and acidosis increased. Repeated nonprotein nitrogen estimations were 175, 250, 210 and 280 mg per 100 cc, with corresponding carbon dioxide estimations of 10.6, 14.7, 13.4 and 17.5 milliequiv per liter. He died on the tenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR FLETCHER H COLBY: May we see the x-ray films?

DR STANLEY M WYMAN: The heart shows enlargement, chiefly of the left ventricle. The aorta is unusually tortuous for a man of this age. The appearance suggests hypertension. There is an

area of ill defined, hazy density in the middle thirds of both lung fields, with slight accentuation of the basilar markings. No unusual soft-tissue masses are visible in the film of the abdomen, and there are no unusual areas of calcification.

DR COLBY Can you make out the renal outlines at all?

DR WYMAN I cannot make them out with certainty.

DR COLBY You cannot say whether or not they are enlarged?

DR WYMAN Not with enough certainty to rely on. My guess is that they may be slightly small.

DR COLBY The fact that a large catheter passed more easily than a small one is of no great significance—it is not unusual for a patient to have enough spasm of the sphincter muscles for that to happen. The subsequent bleeding into the bladder is not unusual. Any overdistended bladder may bleed in this manner when rapidly emptied.

When the patient entered the hospital he obviously was critically ill. All the signs and symptoms that we are given point to a lesion of the heart, as well as to some degree of urethral obstruction and certainly to severe renal damage. All these signs and symptoms may be integrated, although I cannot be certain.

Let us take up the obstructive feature first. The first possibility is some sort of congenital abnormality, which should have made itself evident before the age of forty-nine, however. Such lesions as congenital valves and congenital stricture of the urethra occur in young persons and become evident before this age. A stricture of the urethra can be eliminated by the fact that the patient had nothing in the past history to suggest it, and in the Emergency Ward he was easily catheterized. A catheter cannot be passed easily by a stricture of any severity.

Does a patient of forty-nine have benign hypertrophy of the prostate? He may. I recently operated on a man of forty-nine who had a definitely obstructed prostate with a stone in the bladder. I said, "You are young to have this." And he answered, "I know it, my brother is fifty, and last year he had his prostate operated on."

This man entered the hospital because of difficulty in urinating and with a past history of weakness and hesitancy of the stream. Certainly, prostatic hypertrophy is a definite possibility, and probably infection as well. The dyspnea, wheezing and cough, if not asthmatic (and apparently they were not), suggest cardiac disease. This is confirmed by the systolic murmur, distended neck veins, pulmonary congestion and left ventricular hypertrophy. We can therefore say that he had hypertensive heart disease. One thing that bothers me a good deal is the fact that the blood pressure was 120 systolic, 80 diastolic, and a week later 175 systolic, 90 diastolic. Is that correct?

DR EDWARD F. BLAND Not quite. On admission it was 200 systolic, 100 diastolic.

DR COLBY There was not the change from 120 to 175 systolic in a week?

DR BLAND A later reading was 165 systolic, 90 diastolic, and as the patient became sicker the pressure was lower.

DR FREDERICK C. GOETZ The blood pressure was 125 systolic, 70 diastolic, about a week before he entered the hospital, according to his doctor.

DR COLBY Was he pretty sick then?

DR GOETZ Yes, he was.

DR COLBY The general signs and symptoms are those of a marked degree of renal damage in a patient who was not able to concentrate urine above 1014. He had a low specific gravity of urine with albumin, a low serum calcium, a high phosphorus and marked anemia. The marked anemia must mean a disease of long standing. The hemoglobin was 5 gm. He also had eye signs and edema. It seems unlikely to me that such a degree of renal change in a man of forty-nine could have been associated with a hypertrophied prostate so that I think we have to look for the chief lesion in the kidneys.

What sort of lesion could it have been? The lack of pain in the past and the other symptoms seem to eliminate a certain number of renal lesions, such as hydronephrosis and calculus disease, and the obstructive lesions that affect the upper urinary tract. On the other hand this must have been a bilateral affair, and it seems to me that the most likely possibility is a severe degree of chronic pyelonephritis. This is borne out by the urinary findings, the low specific gravity, the edema, the obviously failing renal function, the eventual acidosis and death and uremia. He had a mixed infection, staphylococcus and colon bacilli in the urine, which is quite consistent with marked pyelonephritis. Acute pyelonephritis is much more apt to have only one organism.

One condition that I cannot rule out, although I have no evidence to favor it except a pair of kidneys that were failing, is bilateral polycystic disease, which is always a possibility. This man was at the age when polycystic disease is apt to make itself evident. There was nothing in the past history to suggest it, however, such as back pain, gradual rise in blood pressure and attacks of gross hematuria. But I cannot eliminate the possibility. That is why I asked particularly about the x-ray findings, to see if we could get any additional information from Dr. Wyman.

My diagnoses are therefore hypertensive heart disease, benign hypertrophy of the prostate and uremia due to pyelonephritis. The patient probably had a pair of lungs that showed quite a bit of edema.

DR TRACY B. MALLORY Can you add anything, Dr. Bland?

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DR. STANLEY M. WYMAN: The heart shows enlargement, chiefly of the left ventricle. The aorta is unusually tortuous for a man of this age. The appearance suggests hypertension. There is an

with a definitely smooth, normal-appearing mucosa over it, elevated above the surrounding mucosa by about 1 to 1.5 cm. There was very little distortion of the peristaltic wave. No ulcer was visible on its surface.

An operation was performed on the ninth hospital day.

#### DIFFERENTIAL DIAGNOSIS

**DR CLAUDE E. WELCH:** This is the record of a patient with a gastric lesion of an undetermined type with incidental hypertension, a mastectomy scar and varicose veins. The history of jaundice is very equivocal, and no further signs or symptoms later developed to implicate the biliary tract. The only other abnormal feature in the history or physical examination is that of slight edema of both lower legs. Since this patient was subjected to no further examination to clarify the cause of the edema, with the exception of one negative examination of the urine, I believe that we can dismiss this symptom as inconsequential.

We have, then, a history of anorexia that began ten months before admission. This was more or less persistent and was followed by epigastric pain at an indefinite date. The history is also very suggestive of an anemia due to blood loss that developed three months before entry.

The diagnosis of prepyloric ulceration was first made about six weeks prior to entry. It may be assumed that following this discovery the patient was treated for a peptic ulcer. However, the filling defect persisted, and was observed at a second examination six weeks later. This filling defect was again observed when the patient entered the hospital.

The presence of achlorhydria that was persistent despite the injection of histamine is of great importance, since nearly 50 per cent of the patients with this finding and a gastric ulceration are found on pathological examination of the resected specimens to have cancer of the stomach.

The x-ray and gastroscopic findings were as usual somewhat at variance. Both of them suggest a submucosal lesion on the lesser curvature in the antral area. However, the presence of ulceration that was noted three times on the x-ray examination was not observed by the gastroscopist. Under these circumstances and in this location, I favor the x-ray description and consider it definite that this patient had an ulcerating lesion. That it was associated with a submucosal mass is quite likely, but not nearly so important as the presence of the ulceration itself.

There are only a few diagnoses to be considered. The ulcer must have been a benign gastric ulcer, carcinoma or the tiny ulceration that is frequently found over pancreatic rests or spindle-cell tumors. The evidence of a submucosal mass could point to a spindle-cell tumor, a pancreatic rest or a tumor that is projecting into the wall of the stomach from

the lesser peritoneal cavity. In this location, of course, the most likely source is the pancreas. It will be noted that the ulceration appeared on x-ray study prior to the time that the larger filling defect first appeared. It could therefore have represented an extension of carcinoma into the submucosal area or even outside the stomach.

The salient features of a prepyloric lesion of short duration developing in a patient in the older age group, the ulceration being associated with complete achlorhydria and failing to heal under at least six weeks of medical treatment, all point to the diagnosis of carcinoma of the stomach rather than to benign ulcer or the rarer tumors mentioned above.

**DR MILFORD D. SCHULZ:** All films made of the stomach show a sharply delimited defect on the lesser-curvature side of the antrum, measuring only a few centimeters across. The mucosal pattern stops abruptly at the defect, which looks as though it is caused by a smooth mass projecting into the stomach lumen. I am not certain about the ulceration described—it may be just barium caught in a fold. If there is ulceration, it must be in a tumor mass, but whether the tumor is intraluminal or intramural is not certain, though from the films I should suspect the tumor to be intraluminal.

Incidentally, there is a small diverticulum of the duodenum lying just oast to the antral defect.

**DR EDWARD B. BENEDET:** It interests me that Dr. Welch should say that the x-ray and gastroscopic findings were "as usual" somewhat at variance. As a matter of fact, in the easy cases they usually agree, in the difficult ones they may not. In a review of 298 cases of gastric carcinoma, gastric ulcer, jejunal ulcer, gastritis, benign tumor, lymphoma, sarcoma, metastatic carcinoma and normal stomach studied by x-ray and gastroscopy and proved by pathological examination, it was demonstrated that the radiologist and gastroscopist agreed in more than half the cases.<sup>1,2</sup> It was also shown that, provided the gastroscopist obtains a good view of the lesion, his chances of reaching a correct diagnosis are greater than those of the radiologist. In this case the view was good, and there was no doubt in my mind that the lesion was submucosal. In my experience, nonulcerating submucosal tumors of the stomach have always been benign, with the exception of 1 case of carcinoma of the pancreas invading the stomach submucosally. Because of the vomiting, the proximity of the tumor to the pylorus and the possibility of cancer I felt that the lesion should be resected. If pathological study of the resected specimen demonstrates an ulcerating tumor, it shows how easy it is for the gastroscopist to miss an ulcer in or beyond a tumor. If, however, this proves to be a nonulcerating malignant submucosal tumor of the stomach, I believe it is exceptional. Whatever the pathological report, it is usually wise to

of biologic knowledge and medical treatment, have been clearly shown by Professor H J Muller,<sup>1, 2</sup> to produce deleterious hereditary mutations. The physician is interested in the welfare of the individual, but the scope of his activities and concerns must include the race if he is to avoid the reproach of the eugenicists that his efforts lead to the final injury of the race. In this, human beings are not exempt from the dangerous results of the advances of science in general.

What is of great importance both theoretically and practically is that a misleading dichotomy must now be discarded — namely, that hereditary and environmental agencies are separable in any complete sense. Germ plasma, the substances of ovum and sperm, is relatively stable, but that stability depends on a stable environment. The inner environment, such as the blood stream, is as necessary to the germ plasma as to the cells of other tissues and organs of the body. There is a vast experimental literature on this subject, including the influence of the vitamins, especially A and E, on the maturation and health of sperm and ovum, that is incontestable.<sup>3-12</sup>

Moreover, Mendelian heredity is fast becoming only a part of genetic knowledge. We are passing into a phase of great scientific advance, involving the physiology and biochemistry of the genes and of the cytoplasm of the gonads as well.<sup>13</sup> The nucleoproteins,<sup>14</sup> for example, are as basic in transmitting the qualities of hereditary nature as they are in the life history of the individual cell and of the body as a whole.

Of further practical importance is the fact that environmental forces can be so focused on the developing embryo as to produce what appears to be a mutation, the so-called phenocopy of Gold-

schmidt.<sup>15</sup> Recently, Wesselhoeft<sup>16</sup> pointed out that German measles, a relatively mild infection, produces an appalling amount of deficiency in the children of mothers who acquired the infection early in pregnancy. This brings to medical attention the extremely important question of the role of "blastophthoria," a term that means merely sick or injured germ plasma as the source of deficiency in human beings. This concept was introduced by Forel<sup>17</sup> and emphasized by Myerson<sup>18</sup> as a theoretic constitutional basis for mental disease, but the geneticists have rather loftily dismissed it as unimportant. Muller's work, which is the great climax of similarly directed investigations, shows that the germ plasma does not dwell in a sanctum sanctorum, but can be destroyed, injured and deviated from normal

functioning by the universe of penetrating forces in which it dwells.<sup>19</sup>

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## TO THE FELLOWS OF THE MASSACHUSETTS MEDICAL SOCIETY

On behalf of the trustees I welcome to membership in the Boston Medical Library all of you who are not already numbered among its fellows.

The Boston Medical Library is one of the leading institutions of its kind in the country. On its shelves are over 200,000 volumes and its collection of periodicals in many languages is outstanding. We wish this great library to be at the service of every physician in Massachusetts, and the share of your increased membership dues that has been allocated to it will make such a goal possible.

We hope that you will show your interest in the Library by visiting it and making use of its facilities.

WALTER G PHIPPEN  
President

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## MASSACHUSETTS MEDICAL SOCIETY

### TREASURER'S OFFICE

All members should be reminded that the proportion of the refund returned to each district society is based on the number of dues paid by March 1 in that district, and also that the names of members who have not paid their dues by March 1 are automatically removed from the mailing list of the *Journal* until such dues are paid. This year \$8000 is being returned to the district societies rather than \$4000 as heretofore.

ELIOT HUBBARD, JR., *Treasurer*

### DEATHS

CRUFF—Frederick E. Cruff, M.D. of Norwell died on January 18. He was in his fifty-third year.

Dr. Cruff received his degree from Harvard Medical School in 1920. He was a member of the Association of Military Surgeons.

His widow and a daughter survive.

HUNT—Ernest L. Hunt, M.D. of Worcester, died on January 17. He was in his seventy-first year.

Dr. Hunt received his degree from Harvard Medical School in 1902. He was surgeon-in-chief of Fairlawn Hospital and director of Worcester Health Department laboratories and was formerly associate medical examiner for Worcester County. He served as a medical officer in World War I. He was a member of the New England Surgical Society and the American Urological Association and a fellow of the American College of Surgeons and the American Medical Association.

His widow, three daughters, a son and nine grandchildren survive.

JONES—Raymond C. Jones, M.D. of Fitchburg died on December 2. He was in his sixty-seventh year.

Dr. Jones received his degree from University of Vermont College of Medicine in 1902.

His widow and a sister survive.

KING—Connie H. King, M.D. of Duxbury died on January 22. He was in his forty-first year.

Dr. King received his degree from University of Tennessee College of Medicine in 1929. He was assistant medical examiner for Plymouth County and chief aesthetist at Jordan Hospital, Plymouth.

His widow, a son, a daughter, two brothers and a sister survive.

McMILLAN—Archibald McMillan, M.D. of Athol died on January 16. He was in his seventy-sixth year.

Dr. McMillan received his degree from Bowdoin Medical School in 1904.

PENDOLA—Anthony S. Pendola, M.D. of Holyoke died on January 10. He was in his fifty-eighth year.

Dr. Pendola received his degree from Middlesex University School of Medicine in 1920. He was a member of the staffs of Providence and Holyoke hospitals and was assistant city physician.

His widow, three brothers and two sisters survive.

## POSTGRADUATE LECTURE COURSE

The third Postgraduate Lecture Course, which has been arranged by the Committee on Postgraduate Medical Education, Massachusetts Medical Society, in co-operation with the Massachusetts Department of Public Health, will begin on March 8. The meetings will be held at Sanders Theater in Memorial Hall, Harvard University, Cambridge. These lectures are designed for all physicians of Massachusetts and surrounding states, medical officers, hospital residents, interns, medical students and postgraduate students.

All those who plan to attend but have not enrolled should do so immediately by either returning the post card recently forwarded to all physicians in Massachusetts or addressing a post card or letter directly to Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston 15.

The detailed program for the course is as follows (no buffet suppers will be served this year)

**Monday March 8 EARLY DIAGNOSIS AND TREATMENT OF CANCER.** Chairmen: Charles C. Lund and Ira T. Nathan

5:55-6:00 OPENING REMARKS Edward P. Bagg, president, Massachusetts Medical Society

6:00-6:40 Cancer of the Oral Cavity William S. MacComb, attending surgeon, Memorial Hospital, New York City

6:40-7:05 Cancer of the Larynx and Pharynx. Leroy A. Schall, chief Oto-Laryngological Service, Massachusetts Eye and Ear Infirmary, professor of laryngology and otology, Harvard Medical School

7:05-7:35 Cancer of the Lung E. D. Churchill, chief West Surgical Service, Massachusetts General Hospital

7:35-8:05 Cancer of the Esophagus Richard H. Sweet, visiting surgeon, Massachusetts General Hospital, surgeon, Palmer Memorial Hospital, instructor in surgery, Harvard Medical School

8:05-8:30 Cancer of the Stomach Arthur W. Allen, chief East Surgical Service, Massachusetts General Hospital, lecturer in surgery, Harvard Medical School

8:30-9:00 Cancer of the Colon and Rectum Richard B. Cattell, surgeon, Lahey Clinic, New England Baptist Hospital and New England Deaconess Hospital

**Wednesday March 10 EARLY DIAGNOSIS AND TREATMENT OF CANCER.** Chairmen: Charles C. Lund and Ira T. Nathan

3:00-3:45 Cancer of the Breast—Diagnosis and Surgical Aspects C. D. Haagenboom, assistant professor of surgery, College of Physicians and Surgeons, Columbia University, New York City

3:45-4:30 Cancer of the Breast—Radiation Aspects M. Lenz, chief Radiological Department, Presbyterian Hospital, New York City, professor of clinical radiology, College of Physicians and Surgeons, Columbia University, New York City

4:30-5:15 Cancer of the Cervix—Early Diagnosis Paul Younge, visiting surgeon, Free Hospital for Women, Brookline

5:15-6:00 Cancer of the Cervix and Endometrium Joe V. Mengs, chief Gynecological Service, Massachusetts General Hospital, clinical professor of gynecology, Harvard Medical School



**Monday, March 15** **CARDIOVASCULAR DISEASES** Chairmen Paul D White and Louis Wolff

6 00-6 25 **Examination of the Patient with Heart Disease** Louis Wolff, associate in medicine, Harvard Medical School, visiting physician, Beth Israel Hospital, consultant in cardiology, Beth Israel Hospital

6 25-6 50 **Roentgenology — Its Value in Cardiac Diagnosis** Felix F Fleischner, director, X-ray Department, Beth Israel Hospital, instructor in radiology, Harvard Medical School and Tufts College Medical School

6 50-7 15 **Electrocardiography Today** Conger Williams, assistant in medicine, Harvard Medical School, consultant in diabetes, Boston Lying-in Hospital

7 15-7 30 **Intermission**

7 30-8 00 **Symptoms of Heart Disease** S A Levine, assistant professor of medicine, Harvard Medical School, physician, Peter Bent Brigham Hospital

8 00-8 30 **The Use of Digitalis** A S Freedberg, associate visiting physician, associate in medical research, Beth Israel Hospital, associate in medicine, Harvard Medical School

8 30-9 00 **Treatment of Myocardial Failure** Paul D White, clinical professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital

**Wednesday, March 17** **EPIDEMIC DIARRHEA IN INFANTS** Chairmen Clement A Smith and Nathan B Talbot

3 00-3 30 **Present Concepts of Etiology** John F Enders, associate professor of bacteriology and immunology, Harvard Medical School, chief, Research Division of Infectious Diseases, Children's Hospital

3 30-4 00 **Epidemiologic Management** Clement A Smith, assistant professor of pediatrics, Harvard Medical School, chief, Infants' Hospital

4 00-4 30 **Clinical Management** Allan M Butler, professor of pediatrics, Harvard Medical School, chief, Children's Medical Service, Massachusetts General Hospital

4 30-6 00 **Open Forum** Drs Butler, Smith, Talbot and Enders

**Monday, March 22** **ARTHRITIS** Chairmen Theodore B Bayles and Charles L Short

6 00-6 20 **Classification of Joint Disease** Charles L Short, associate physician, Massachusetts General Hospital

6 20-6 50 **The Diagnostic Value of Synovial Fluid Examination** Marian W Ropes, assistant professor of medicine, Harvard Medical School, associate physician, Massachusetts General Hospital

6 50-7 20 **Rheumatoid Spondylitis Recognition and Treatment** J Sydney Stillman, assistant in medicine, Harvard Medical School, physician-in-chief, Robert Breck Brigham Hospital

7 20-7 30 **Intermission**

7 30-8 00 **Gout** Walter Bauer, associate professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital

8 00-8 30 **Shoulder-Hand Syndromes** Theodore B Bayles, assistant in medicine, Harvard Medical School, visiting physician, Robert Breck Brigham Hospital, chief, Arthritis Clinic, Peter Bent Brigham Hospital

8 30-9 00 **Nonsurgical Orthopedic Care of Arthritic Joints** Theodore A Potter, instructor in orthopedic surgery, Boston University School of Medicine, visiting orthopedic surgeon, Robert Breck Brigham and Massachusetts Memorial Hospitals

**Wednesday, March 24** **INFECTIOUS DISEASES** Chairmen Maxwell Finland and Charles A Janeway

**PART I**

3 00-3 20 **Indications and Uses of Vaccines and Antisera** Geoffrey Edsall, director, Division of Biologic Laboratories, assistant professor of public-health bacteriology, Harvard School of Public Health

3 20-3 40 **Hemolytic-Streptococcus Infections** Louis Weinstein, assistant professor of medicine, Boston University School of Medicine, instructor in infectious diseases, Harvard Medical School, physician and chief-of-service, Haynes Memorial Hospital

3 40-4 00 **Rheumatic Fever** David Rutstein, visiting physician, Children's Hospital and House of the Good Samaritan, consultant in preventive medicine, Peter Bent Brigham Hospital and Massachusetts General Hospital, professor of preventive medicine, Harvard Medical School

4 00-4 15 **Discussion**

**PART II**

4 15-4 35 **Clinical Aspects of Virus Diseases** Conrad Wesselschoft, professor of clinical medicine, Boston University School of Medicine, professor of communicable diseases, Harvard Medical School and Harvard School of Public Health

4 35-4 55 **Newer Methods in the Diagnosis of Specific Virus Diseases** F Sargent Choccy, assistant professor of bacteriology, Harvard Medical School

4 55-5 00 **Discussion**

**PART III**

5 00-5 30 **The Diagnosis of Obscure Fever** Chester S Keefer, professor of medicine, Boston University School of Medicine, director, Evans Memorial, Massachusetts Memorial Hospitals

5 30-6 00 **Progress in Pulmonary Tuberculosis** Dr Donald S King, lecturer in medicine, Harvard Medical School, physician, Massachusetts General Hospital

**Monday, March 29** **NEUROLOGY** Chairmen Derek E Denny-Brown and Charles S Kubik

6 00-6 40 **The Place of Thymectomy in the Treatment of Myasthenia Gravis** Henry R Vicks, lecturer on neurology, Harvard Medical School, neurologist, Massachusetts General Hospital

6 50-7 30 **Clinical Varieties of Multiple Neuritis** Derek E Denny-Brown, James Jackson Putnam Professor of Neurology, Harvard Medical School, director, Neurological Unit, Boston City Hospital

7 40-8 20 **The Place of Penicillin in the Treatment of Neurosyphilis** Raymond D Adams, assistant professor of neurology, Harvard Medical School, lecturer in neurology, Tufts College Medical School, visiting neurologist and neuropathologist, Boston City Hospital

8 20-9 00 **Diagnosis of Spinal-Cord Compression** Charles S Kubik, chief, Neurological Service, Massachusetts General Hospital, professor of medicine, Harvard Medical School

**Wednesday, March 31** **DERMATOLOGY** Chairmen John G Downing and Jacob H Swartz

3 00-3 30 **Treatment of Bacterial, Virus and Parasitic Diseases of the Skin** Francis Thurmon, clinical professor of dermatology, Tufts College Medical School

3 30-4 00 **Treatment of Psoriasis, Seborrhea and Nutritional Diseases** Bernard Appel, clinical professor of dermatology, Tufts College Medical School

4 00-4 30 **Treatment of Fungus Diseases of the Skin** Jacob H Swartz, assistant professor of dermatology, Harvard Medical School and Postgraduate School

4 30-5 00 **Dermatologic Allergy, Including Drug Eruptions** G Marshall Crawford, acting head, Department of Dermatology, Harvard Medical School

5 00-5 30 **Cutaneous Manifestations of Systemic Diseases** John G Downing, professor of dermatology, Boston University School of Medicine and Tufts College Medical School

5 30-6 00 **Question Period**

**Monday April 5 ALLERGY** Chairmen Jeremiah E. Greene and Francis C. Lowell

6:00-6:45 **Allergy—Its Scope and Place in Medicine** Walter S. Burrage, assistant physician, Massachusetts General Hospital, physician New England Deaconess Hospital, assistant in medicine, Harvard Medical School

6:45-7:30 **The Treatment of Asthma with Drugs** Francis C. Lowell, associate professor of medicine, Boston University School of Medicine, chief, Allergy Clinic, Out Patient Department, Massachusetts Memorial Hospitals

7:30-7:40 **Intermission**

7:40-8:15 **Skin Tests and Injection Therapy in Hay Fever and Asthma** Jeremiah E. Greene, affiliated with Massachusetts General Hospital, Mt. Auburn Hospital, Newton-Wellesley Hospital and New England Baptist Hospital

8:15-9:00 **The Antihistaminic Drugs** Francis C. Lowell, associate professor of medicine, Boston University School of Medicine, chief of Allergy Clinic, Out Patient Department, Massachusetts Memorial Hospitals

**Wednesday April 7 OFFICE PROCEDURES IN DISEASES OF MOUTH, VAGINA AND RECTUM** Chairmen Walter B. Hoover, Roy E. Mabrey and Francis P. McCarthy

3:00-3:20 **Lesions of the Oral Mucosa** Francis P. McCarthy, professor of oral medicine, Tufts College Dental School, lecturer in dermatology and syphilology, Tufts College Medical School

3:20-3:40 **Lesions of the Hard Parts of the Oral Cavity** Joseph F. Volker, dean and professor of clinical dentistry, Tufts College Dental School

3:40-4:00 **Lesions of the Oropharynx** Walter B. Hoover, chief, Department of Nose and Throat, Lahey Clinic

4:00-4:10 **Intermission**

4:10-4:35 **The Vaginal Smear in the Diagnosis of Carcinoma of the Uterus** Howard Ulfelder, assistant in surgery, Massachusetts General Hospital

4:35-5:00 **Displacements of the Uterus** Louis E. Phaneuf, professor of gynecology, Tufts College Medical School, chief, Department of Gynecology, Carney Hospital

5:00-5:20 **Methods of Diagnosis of Anorectal Diseases** Roy E. Mabrey, assistant surgeon, Massachusetts General Hospital

5:20-5:40 **The Problem of Rectal Bleeding** Neil W. Swinton, surgeon, Lahey Clinic, New England Deaconess Hospital and New England Baptist Hospital

5:40-6:00 **Premalignant and Malignant Lesions of Rectum and Colon** E. Parker Hayden, chief, Proctologic Clinic and assistant visiting surgeon, Massachusetts General Hospital

**Monday, April 12 CLINICAL ROENTGENOLOGICAL, PATHOLOGICAL SESSION** Chairman Merrill C. Sosman (who will present the Case Reports)

6:00-7:00 **Bone Diseases** William T. Green, orthopedic surgeon, Peter Bent Brigham Hospital, visiting orthopedic surgeon, Children's Hospital, assistant professor of orthopedic surgery, Harvard Medical School, Sidney Farber, pathologist, Children's Hospital, assistant professor of pathology, Harvard Medical School

7:00-8:00 **Chest Diseases** Cutting B. Favour, associate in medicine, Harvard Medical School, associate in medicine, Peter Bent Brigham Hospital, and Alan Moritz, pathologist, Peter Bent Brigham Hospital, professor of legal medicine, Harvard Medical School

8:00-9:00 **Endocrine Problems** Lewis M. Hurstthal, director, Department of Medicine, Lahey Clinic, and S. Burt Wolbach, pathologist-in-chief, Children's Hospital, Shattuck Professor of Pathology, Harvard Medical School

**Wednesday April 14 GASTROENTEROLOGY** Chairmen Benjamin M. Banks and James A. Halsted

3:00-3:20 **Functional Gastrointestinal Disorders—Principles of Management** James A. Halsted, physician-in-chief, Faulkner Hospital

3:20-3:45 **The Role of the Internist in the Management of Chronic Ulcerative Colitis** Benjamin M. Banks, chief, Gastrointestinal Clinic and associate visiting physician, Beth Israel Hospital

3:45-4:10 **The Role of the Psychiatrist in the Management of Chronic Ulcerative Colitis** Erich Lindemann, psychiatrist, Massachusetts General Hospital

4:10-4:35 **The Role of the Surgeon in the Management of Chronic Ulcerative Colitis** Leland S. McKitt, visiting surgeon, Massachusetts General Hospital

4:35-4:45 **Intermission**

4:45-5:10 **The Differential Diagnosis of Dysphagia** Seymour Gray, senior associate in medicine, Peter Bent Brigham Hospital

5:10-5:35 **Surgical Treatment of Carcinoma of the Esophagus and Cardiac End of the Stomach** Richard H. Sweet, visiting surgeon, Massachusetts General Hospital

5:35-6:00 **Discussion**

**Tuesday, April 20 (Note change from Monday, April 19) ENDOCRINE AND DIABETES.** Chairmen Frank N. Allan and Joseph C. Aub

6:00-6:30 **Treatment of Diabetic Coma** Allan M. Butler, professor of pediatrics, Harvard Medical School

6:30-7:00 **Endocrine Complications of Diabetes** Frank N. Allan, associate director, Medical Department, Lahey Clinic

7:00-7:30 **Sex Hormones in Growth** Joseph C. Aub, professor of research in medicine, Harvard Medical School

7:30-8:00 **Menstrual Disorders** John Rock, clinical professor of gynecology, Harvard Medical School

8:00-8:30 **The Theoretical Background of Therapy of the Thyroid** J. H. Means, Jackson Professor of Clinical Medicine, Harvard Medical School

8:30-9:00 **Studies on Acromegaly** Fuller Albright, associate professor of medicine, Harvard Medical School

**Wednesday, April 21 PSYCHIATRY** Chairmen Robert E. Fleming and Harry C. Solomon

3:00-3:30 **Psychiatric Procedure and Technique** Harry C. Solomon, professor of psychiatry, Harvard Medical School

3:30-4:00 **Adjustment Problems of the Pre-school Child** Marian C. Putnam, director, The James Jackson Putnam Children's Center

4:00-4:30 **Psychiatric Problems of the Adolescent** George E. Gardner, executive director, Judge Baker Guidance Center

4:30-5:00 **Psychiatric Problems of Young Men** Gaylord P. Coon, psychiatrist, Department of Hygiene, Harvard University

5:00-6:00 **Psychiatric Aspects of Acute Grief** Erich Lindemann, psychiatrist, Massachusetts General Hospital

**Monday April 26 CONVULSIVE SEIZURES.** Chairmen William G. Lennox and Maxwell E. MacDonald

6:00-6:30 **Differential Diagnosis and Etiology** William G. Lennox, visiting neurologist, Boston City Hospital, assistant professor of neurology, Harvard Medical School

6:30-7:10 **Neurosurgical Considerations and Treatment** Wilder Penfield, Montreal, Canada, professor of neurology and neurosurgery, McGill University, Montreal

7 10-7 50 **Medical and Drug Therapy** H Houston Merritt, professor of clinical neurology, Columbia University College of Physicians and Surgeons, New York City

7 50-8 20 **Psychological and Social Problems and Treatment** Maxwell E Macdonald, professor of neurology, Harvard Medical School, senior neurologist, Boston City Hospital

8 20-9 00 **Question Period**

**Wednesday, April 28 BLOOD DISEASES** Chairmen William Dameshek and John W Norcross

#### PART I THE DIAGNOSIS AND TREATMENT OF HEMORRHAGIC DISEASE

3 00-3 30 **Diagnostic Tests** Jacob Neber, assistant in hematology, Joseph H Pratt Diagnostic Hospital

3 30-4 00 **The Purpuras** Charles S Davidson, associate in medicine, Harvard Medical School, junior visiting physician, Boston City Hospital

4 00-4 30 **Hemophilia** Benjamin Alexander, instructor in medicine, Harvard Medical School, visiting physician and associate in medical research, Beth Israel Hospital

#### PART II SYMPOSIUM ON TREATMENT

4 30-5 00 **Treatment of Anemia** Donat Cyr, assistant hematologist, Department of Medicine, Lahey Clinic

5 00-5 30 **Chemotherapy of Leukemia and Lymphoma** William Dameshek, professor of clinical medicine, Tufts College Medical School, consultant in hematology and visiting physician, Joseph H Pratt Diagnostic Hospital

5 30-6 00 **Splenectomy in Blood Disorders** John W Norcross, hematologist, Department of Medicine, Lahey Clinic

**Monday, May 3 GENITOURINARY DISEASE** Chairmen J Hartwell Harrison and George C Prather

6 00-6 30 **Hematuria Significance and Management** J Hartwell Harrison, senior associate in genitourinary surgery, Peter Bent Brigham Hospital, associate professor of genitourinary surgery, Harvard Medical School

6 35-7 00 **Pain Interpretation relative to genitourinary causes** George C Prather, visiting neurologic surgeon, Boston City Hospital, instructor in genitourinary surgery, Harvard Medical School

7 10-7 40 **Streptomycin in the Treatment of Non-tuberculous Bacillary Urinary Infections** Maxwell Finland, physician-in-chief, Fourth Medical Service, Boston City Hospital, assistant professor in medicine, Harvard Medical School

7 45-8 15 **The Diagnosis and Treatment of Cancer of the Prostate** Wyland F Leadbetter, assistant professor in genitourinary surgery, Harvard Medical School, clinical professor of urology, Tufts College Medical School, associate visiting urologist, Massachusetts General Hospital

8 20-8 50 **Present Outlook in Carcinoma of the Bladder** Roger C Graves, clinical professor of urology, Tufts College Medical School, urologist-in-chief, Carney Hospital

**Wednesday, May 5 OBSTETRICS** Chairmen Duncan E Reid and Benjamin Tenney, Jr

#### PART I DIABETES MELLITUS IN PREGNANCY

3 00-3 25 **Medical Treatment** David Hurwitz, assistant instructor in medicine, Harvard Medical School, consultant in diabetes, Boston Lying-in Hospital

3 25-3 45 **Endocrinological Treatment** Olive Smith, Ph D, director, Fearing Research Laboratory, Free Hospital for Women

3 45-4 00 **Question Period**

#### PART II HEART DISEASE IN PREGNANCY

##### A TWENTY-FIVE-YEAR REVIEW

4 00-4 25 **Treatment** Burton Hamilton, clinical associate, Thorndike Memorial Laboratory, Boston City Hospital, instructor, graduate courses, Harvard Medical School

4 25-4 30 **Question Period**

#### PART III HYPERTENSION IN PREGNANCY

4 30-4 55 **Medical Aspects** Lewis Dexter, associate in medicine, Peter Bent Brigham Hospital and Harvard Medical School

4 55-5 15 **Obstetrical Aspects** Benjamin Tenney, associate professor of obstetrics, Boston University School of Medicine, assistant obstetrician, Massachusetts General Hospital

5 15-5 30 **Question Period**

#### PART IV VAGINAL BLEEDING IN LAST TRIMESTER OF PREGNANCY

5 30-5 45 **Clinical Aspects** H Bristol Nelson, senior obstetrician, Boston Lying-in Hospital, professor of gynecology and obstetrics, Harvard Medical School

5 45-5 55 **Pathological Aspects** Arthur T Hertig, assistant professor of obstetrics and assistant professor of pathology, Harvard Medical School, pathologist, Free Hospital for Women, obstetrician, Out-Patient Department, Boston Lying-in Hospital

5 55-6 00 **Question Period**

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### REVIEW OF COMMUNICABLE DISEASES IN 1947

The year 1947 was very favorable regarding the general prevalence of communicable diseases. The total number of cases reported to the Department—76,469—was the lowest reported since 1916, the lowest figure in recent years being 78,089 cases in 1938. The low figure for 1947, however, can be attributed largely to the low prevalence of some of the less serious diseases of childhood. Both measles and German measles were much below normal. Scarlet fever reached the lowest level since 1905. On the other hand, the record for 1947 would have been still lower had not chicken pox reached the second highest figure since the disease was reportable, and mumps and whooping cough maintained about the normal prevalence.

Meningococcal meningitis, lobar pneumonia and typhoid fever were at very low levels, and gonorrhea and syphilis showed some decline. Bacillary dysentery, poliomyelitis and salmonellosis were at about the normal prevalence. On the other hand, diphtheria, tularemia, trichinosis and undulant fever all showed an increase.

Diphtheria continues to be a trying problem. It was hoped that the increased emphasis on immunization programs would bring the prevalence down, but more cases were reported this year than in 1946, which itself was the highest year since 1934.

On the other hand, not a single case of smallpox was reported, marking the fifteenth year since the disease was prevalent in the State. Typhoid fever dropped to the second lowest level since reporting began.

DISEASE	1947	1946	SEVEN YEAR MEDIAN
Actinomycoma	1	3	3
Anthrax	2	3	3
Chancroid	31	19	20*
Chicken pox	18,791	11,912	11,912
Diphtheria	432	439	151
Dog bite	11,148	11,359	10,701
Dysentery amebic	10	7	4
Dysentery bacillary	188	68	243
Encephalitis, infectious	9	21	21
German measles	932	4,618	2,131
Gonorrhea	3,805	5,062	4,701
Granuloma inguinale	5	4	4*
Hookworm	2	3	0
Lymphocytic choriomeningitis	4	7	4
Lymphogranuloma venereum	8	10	31*
Malaria	91	509	116
Measles	12,069	38,400	338
Meningitis meningococcal	5	116	161
Meningitis, Pfeiffer bacillus	18	18	17
Meningitis pneumococcal	28	48	48†
Meningitis other forms	1	10	25†
Meningitis undetermined	59	44	44†
Mumps	8,181	5,910	10,491
Ophthalmia neonatorum	599†	485†	591†
Pneumonia, lobar	1,344	1,483	1,104
P. hyaline	346	178	252
Polio	0	2	0
Rabies in animals	0	1	5
Rocky Mountain spotted fever	3	1	0
Salmonellosis	156	160	120
Scarlet fever	4,428	6,079	10,773
Septic sore throat	112	79	79
Syphilis	3,211	4,070	5,074
Tetanus	11	13	14
Trachoma	7	12	9
Trichinosis	59	18	11
Tuberculosis pulmonary	2,640	2,658	2,616
Tuberculosis, other forms	190	179	199
Tuberculosis, bilious	8	10	15
Tulariaemia	7	7	1
Typhoid fever	25	35	34
Typhus fever	0	3	2
Undulant fever	16	52	49
Whooping cough	7,125	6,514	7,415

\*Three year median

†Five year median

‡Includes suppurative conjunctivitis

## MISCELLANY

### APPOINTMENT OF MANFRED BOWDITCH

Manfred Bowditch, formerly field director of the Saranac Laboratory and director of the Division of Occupational Hygiene of the Department of Labor and Industries of the Commonwealth of Massachusetts, has been appointed director of health and safety of the Lead Industries Association. He will make his office at the Association's headquarters, 420 Lexington Avenue, New York City.

### NATIONAL COMMITTEE FOR MENTAL HYGIENE

Dr. Arthur H. Ruggles, former superintendent of the Butler State Hospital, Providence, Rhode Island, has been elected president of the National Committee for Mental Hygiene. Dr. Ruggles, who has been the superintendent of Butler Hospital since 1922, is president of the Emma Pendleton Bradley Home, Providence, and a trustee of Dartmouth College. He is consultant in mental hygiene in the Department of University Health and lecturer in psychiatry at Yale University, a member of the advisory council on research in nervous and mental diseases and consultant, United States Public Health Service, and a member of the advisory council of the Department of Social Welfare of Rhode Island. Dr. Ruggles is a former president of the American Psychiatric Association and of the New England Society for Psychiatry.

### CANCER

A new journal, *Cancer*, sponsored by the American Cancer Society, will make its appearance this spring. Every phase of the cancer problem will be covered, with major emphasis on clinical aspects. Dr. Fred W. Stewart, of Memorial Hospital, New York City, will be the editor-in-chief, assisted by an editorial advisory board. Original papers should be sub-

mitted for consideration to the editor, Dr. Fred W. Stewart, 444 East 68th Street, New York 21, New York. *Cancer* will be published bimonthly, at eight dollars a year, by Paul B. Hoeber Incorporated, Medical Book Department of Harper and Brothers.

## CORRESPONDENCE

### EFFECT OF ENVIRONMENTAL INFLUENCES

To the Editor: Just about twenty five years ago Professor Hermann J. Muller read a paper at the Second International Congress of Eugenics demonstrating that external influences do not increase the mutation rate in animals—in other words, that they have little to do with hereditary processes.

Last year the same distinguished scientist received the Nobel prize for proving that environmental influences especially radiations of various types enormously increase the mutation rate. This in itself is of human interest in that a man completely changed his opinion in twenty five years but what is more important is that Professor Muller has a real deal to say about the danger to the human race from radiations and radioactive substances of all kinds. Since most of the mutations are either lethal or defective, it seems that the damage need not appear at once. His article in the September number of the *Journal of Heredity* culminates in a very portentous warning to the medical profession that the use of radioactive substances may be associated with harm to the race of a kind not at all apparent at once. In fact the front cover of the journal is wholly given over to this warning.

Every man who undertakes the use of radioactive substances of any kind whether for therapy or investigation should read this great geneticist's paper which incidentally was read when he received the Nobel prize. He speaks not only of the dangers of x rays but also of mustard gas and of ultraviolet radiation. We are going ahead rather fast in the use of radiated atoms and molecules in the treatment of disease and also in the investigation of physical processes. It might be well to study the germ plasm—that is the substance of ovary and testicle—at the same time that studies are being carried out on the thyroid gland or whatever part of the body is being bombarded for therapeutic or investigative purposes.

Medicine is in a dangerous position. It has at hand powerful instruments which it often uses without due regard for the welfare of the patient as a whole. Similarly the use of mineral oil for constipation has been assumed to be an innocuous way of regulating one of the functions of the gastrointestinal tract. Now it appears likely that this is a way of preventing the absorption of vitamin A.

171 Bay State Road  
Boston

ABRAHAM MYERSON, M.D.

### DEPRIVATION OF LICENCE

To the Editor: At the meeting of the Board of Registration in Medicine held January 15 the registration of Dr. Daniel Kaplan of Worcester was suspended for three months because of gross misconduct in the practice of his profession.

H. QUINCY GALLUPE, M.D., Secretary  
Board of Registration in Medicine

State House  
Boston

## BOOK REVIEW

*Human Genetics*. By Reginald R. Gates. B.Sc., Ph.D., D.Sc., LL.D. 8° cloth two volumes 1318 pp. with 325 illustrations. New York: Macmillan Company, 1946. \$15.00.

This monumental treatise is essentially a reference work. It is based on the author's previous book *Heredity and Eugenics*, published in 1923, but the number of chapters has been doubled and the amount of material increased fivefold. The relation of heredity to all diseases and abnormalities is discussed in detail. The first chapters deal with the general principles of heredity in man, human cytology and linkage. These are followed by special chapters on the diseases and abnormalities of the various organs and systems and on general diseases and conditions. Of special interest are the chapters on color blindness, albinism, metabolic defects

hemophilia, blood groups, allergy, hereditary syndromes, sexual and intersexual conditions, twins and twinning, cancer, constitution, body build and susceptibility, stature and size and anthropologic characters. The text is well arranged and well written in an easy style. Selected references are appended to each chapter. A comprehensive index concludes the work. The book is well published in every way. It is a delight to read the handsome, clear type on good paper. The treatise is recommended for all medical, scientific, college and public libraries and should prove useful to all physicians.

## NOTICES

### ANNOUNCEMENTS

Dr Louis S Chase announces the removal of his office to 416 Marlborough Street, Boston

Dr Clarke Staples announces the removal of his office to 543 Highland Avenue, Malden

Dr Donald M Stewart announces the opening of an office for the practice of obstetrics and gynecology at 745 Main Street, Fitchburg

### NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held in the amphitheater of the Dowling Building, Boston City Hospital, on Monday, March 1, at 8 15 p m. Dr Laurence B Ellis will preside.

#### PROGRAM

Experience with Dicumarol in Acute Myocardial Infarction. Drs E Bresnick, L B Ellis, H N Hultgren, B Rapoport and H S Sise.

Venous-Pressure Responses to Exercise and Abdominal Compression. Dr H N Hultgren.

Observations on the Heart in Women. Dr B E Hamilton.

Circulatory Dynamics in Myxedema. Drs R A Bloomfield, L B Ellis, W K Long, G Maresh, J G Mebane and J P Milnor.

Evaluation of Vitamin E in the Treatment of Angina Pectoris. Drs I B Ravin and K H Katz.

Two to Three Year Follow-up on Penicillin-Treated Cases of Subacute Bacterial Endocarditis. Dr B Rapoport.

Interested physicians and medical students are cordially invited to attend.

### APPOINTMENT OF COMMISSIONED OFFICERS IN NAVY MEDICAL AND DENTAL CORPS

The statutory authority contained in Public Law 365 of 80th Congress, Title II (Army-Navy-Public Health Service Medical Officer Procurement Act of 1947), makes it possible for civilian doctors to become commissioned officers in the regular Navy, with ranks up to and including that of captain, provided they meet the professional and physical qualifications.

To qualify for appointment a doctor must be a citizen of the United States and a graduate of a Class "A" medical school and must have served at least one year's internship in an approved hospital. Candidates will then be judged on a number of qualifications, such as membership in a specialty board, teaching connections, the number of years of professional or scientific practice and hospital or laboratory connections.

Interested physicians should apply to the Bureau of Naval Personnel, Bureau of Medicine and Surgery, Navy Department, Washington, D C.

### MEDICAL AND SURGICAL POSITIONS IN OVERSEAS ARMY HOSPITALS

Opportunities for advanced training and experience in the various special fields of medicine and surgery in overseas Army hospitals are available. These hospitals are registered

with the American Medical Association, and the training may be acceptable by the specialty board as part of the period usually required to be spent in limited practice and experience prior to admission for examination. Interested members of the medical profession who have completed the formal training requirements for certification in one of the special fields are eligible to apply for these positions.

For information concerning the specialties and the location of hospitals, as well as the terms under which physicians may avail themselves of the training, application should be made to the Surgeon General, United States Army, Washington 25, D C.

### NATIONAL TUBERCULOSIS ASSOCIATION TEACHING AND RESEARCH FELLOWSHIPS

National Tuberculosis Association teaching and research fellowships in the field of tuberculosis are available; it was recently announced. Annual stipends for the fellowships will range from \$2400 to \$3200. Provision will also be made for laboratory fees and similar incidental expenses. The fellowships will be limited to graduates of American schools for teaching and investigation in the United States. Although preference will be given to applicants with a degree of Doctor of Philosophy or Doctor of Medicine, fellowships will not be restricted to the holders of these degrees. Applications will be considered in the fields of pathology and bacteriology, clinical medicine, epidemiology and social and statistical research. Applicants may elect the institutions in which they wish to study.

Persons interested in obtaining a fellowship should write to Dr James E Perkins, managing director, National Tuberculosis Association, 1790 Broadway, New York 19, New York, for further information.

### KENFIELD MEMORIAL FUND SCHOLARSHIP

A scholarship of \$100 will be available in 1948 for training of teachers of deaf adults. Applicants, in addition to being adult residents of the United States should meet the following requirements: personal characteristics necessary for successful teaching, ability to read lips as certified upon examination by an approved instructor in lip reading, a bachelor's degree, or two years of college work or successful experience in teaching in public or private schools, in addition to twelve semester hours of work in adult education, psychology of the handicapped, voice production and control, social service or kindred subjects, and thirty clock hours of private instruction under an approved teacher of lip reading or sixty clock hours of instruction in public-school classes under an approved teacher of lip reading. The winner of the scholarship may take the normal course from any normal training teacher or school or university in the United States offering a course acceptable to the Teachers' Committee of the American Hearing Society. The applicant for the scholarship must be a prospective teacher. Applications from those who are teaching lip reading now cannot be considered. The scholarship must be used within one year from the granting of the award.

Applications must be filed between March 1 and May 1, 1948, with Miss Rose V Feilbach, 2431 14th Street, N W, Washington 9, D C.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 26

##### FRIDAY, FEBRUARY 27

\*9-00-10 00 a m. Clinicopathological Conference. Drs Chester S Keeler and H E MacMahon. Joseph H Pratt Diagnostic Hospital.

\*10 00 a m -12 00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

##### MONDAY, MARCH 1

\*12 15-1 15 p m. Clinicopathological Conference. Peter Bent Brigham Hospital.

##### TUESDAY, MARCH 2

12 00 m. X-Ray Conference. Margaret Jewett Hall, Mt Auburn Hospital, Cambridge.

\*12 15-1 15 p m. Clinicorontgenological Conference. Peter Bent Brigham Hospital.

\*1 30-2 30 p m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

(Notices concluded on page xxvii)

## NOTICES (Concluded from page 278)

## WEDNESDAY MARCH 3

- \*12:00 p.m. Grand Rounds and Clinico-pathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
 \*7:00-8:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services, Children's Hospital

\*Open to the medical profession

JANUARY-APRIL Thirteenth Postgraduate Seminar in Neurology and Psychiatry Metropolitan State Hospital. Page 348 issue of August 28  
 FEBRUARY 21-25 American Hospital Association. Page 136 issue of January 22.

FEBRUARY 25-28 Postgraduate Assembly: Endocrinology. Page 36, issue of January 22.

FEBRUARY 25 Tufts Alpha Omega Alpha. Page 170 issue of January 29  
 FEBRUARY 25 New England Pediatric Society. Page 170 issue of January 29

MARCH 1 New England Heart Association. Page 378  
 MARCH 9 New York Tuberculosis and Health Association. Page 136 issue of January 22.

MARCH 11 Diagnosis and Treatment of Paraneoplastic Jaundice. Dr. Chester M. Jones. Penetucket Association of Physicians. 8:30 p.m. Harkness Hall

MARCH 11 Fiftieth Anniversary of Cornell University Medical College. Page 136, issue of January 22

MARCH 12 and 13 American Association of Pathologists and Bacteriologists. Page 204 issue of February 3

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons American Industrial Hygiene Association American Conference of Governmental Industrial Hygienists American Association of Industrial Nurses Inc. and American Association of Industrial Dentists Hotel Statler Boston

APRIL 7-9 14 and 16 American Trade Society. Page 240 issue of February 12.

APRIL 19-23 American College of Physicians. Page 31 issue of July 31  
 APRIL 22-MAY 2 American Academy of Pediatrics. Page 240 issue of February 12

MAY 6-8 American Association for the Study of Cancer. Page 31 issue of July 31

MAY 16-23 International College of Surgeons. Page 136 issue of January 22

MAY 17-20 American Urological Association. Hotel Statler Boston

MAY 18-22 American Association on Mental Deficiency. Copple Plaza Hotel Boston

MAY 20-25 American Board of Ophthalmology. Page 170 issue of January 29

MAY 25-27 Massachusetts Medical Society Annual Meeting. Hotel Statler Boston

JUNE 28-30 American Academy of Pediatrics. Hotel Schroeder Milwaukee Wisconsin

JULY 12-17 First International Polymyositis Conference. Page 16 issue of January 1

SEPTEMBER 13-15 American Academy of Pediatrics. Olympic Hotel Seattle Washington

SEPTEMBER 29 Mississippi Valley Medical Editors Association. Page 170 issue of January 29

OCTOBER 6-9 American Board of Ophthalmology. Page 170 issue of January 29

NOVEMBER 20-23 American Academy of Pediatrics. Annual Meeting. Chalfonte-Haddon Hall Hotel Atlantic City New Jersey

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

- MARCH 9  
 MAY 11 Annual Meeting. Hotel Weldon, Greenfield  
 All other meetings will be held at the Franklin County Hospital, Greenfield

## MIDDLESEX EAST

- MARCH 24  
 MAY 11 Annual Meeting  
 All meetings will be held at the Belvidere Club, Wakefield

## MORFOLK

- FEBRUARY 24 Obstetric and Gynecologic Night  
 MARCH 23 Harvard Night

## PLYMOUTH

- MARCH 18 Goddard Hospital, Brockton  
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## INTERNAL PUBLIC RELATIONS\*

JAMES RAGLAN MILLER, M.D.†

HARTFORD, CONNECTICUT

IN CONNECTICUT it is a custom for the principal officers of the Medical Society to attend each of the eight county medical association meetings. These occur twice a year, and although riding circuit is an arduous task, it is worth while in the interest of good internal public relations, for the members of the Society are considered the first public. At these meetings the members have a chance to tell the state officers what they believe is wrong and what they suggest should be done about it, and the officers on their part have an opportunity to interest the members, if they can, in the projects of the Society. I am sure that every well organized state society attends to this need in some manner.

I am glad to see developing the habit of having someone from the American Medical Association as a speaker at every state medical society meeting. When Dr. Metcalf was unable to obtain the speaker he desired for this occasion, he turned to me and I told him that I was glad to do what I could. Though I cannot deliver a brilliant oration or provide entertainment with wit and humor, I can perhaps convince you that the Board of Trustees is a very human group. It endeavors to be close to the individual members, and in carrying out the directives and operating under the policies laid down by the House of Delegates, it must at all times bear in mind the effect of its actions on the medical profession in America.

This opportunity allows me to express my high appreciation of the activities of the New Hampshire delegate, Dr. Deering Smith. Anyone who follows the transactions of the House of Delegates of the American Medical Association will learn firsthand the careful attention that is given to his wise counsel.

The aim of any public-relations program should be to promote favorable consideration by the public of the organization and of the product that it offers. The title chosen for this occasion emphasizes the importance of having a sound product, of ample production, and of having a well informed sales

force. The cynic may question, "Why have a sales campaign?" And, indeed, it seems almost unnecessary to ask the public, which has had confidence in the profession for a hundred years or more, to think even more favorably of us. I do not propose to argue the needs of a positive campaign for public approval. It may be said, however, that there is a general opinion that the public holds the individual physician in high regard but is not so clear in its approval of the medical profession as an organization.

I believe that this criticism of organized medicine is losing its force. Most of the bitter criticism comes from those who wish to alter the basic structure of the whole American way of life. Suffice it to say that the House of Delegates has directed that positive steps be taken to place more effectively before the American people the accomplishments of the medical profession and its part in meeting the needs of the people for medical care. Anyone who went to the centennial celebration of the American Medical Association at Atlantic City must have had a feeling of pride as he saw demonstrated the important position that the medical profession occupies in the hearts and minds of the American people.

Today I shall consider some of the things that I believe we can do within our organization better than we have in the past so that our own members to the last man can be proud of the organization, and so that the profession itself may need less often to apologize or to give excuses for the action of any of its members. This is the area of internal public relations, which must be sound if we are to have healthy relations with the public at large.

The American Medical Association is a large federation of state organizations in which the county societies as the basic units occupy a conspicuous position of power and local responsibility. The complex problems and great responsibilities of large county associations whose membership runs into thousands will differ greatly from those handled with comparative ease by a small county association. The small society presents a special problem for its parent organization. For all practical purposes the

\*Presented at the annual meeting of the New Hampshire Medical Society, Newcastle, New Hampshire, June 20, 1947.

†Visiting obstetrician and gynecologist, Hartford Hospital.



state society must function on its behalf and with its co-operation. On the other hand, a large county society may be led by reason of its size and power to usurp some of the legitimate functions of the state organization and to exert undue influence within the state society to the detriment of the small county association. We have had enough of jurisdictional disputes elsewhere, and we do not want them in medicine.

Within the profession there are also many local societies — academies of medicine whose primary interests are in developing scientific programs. Occasionally, a local group of physicians organizes for purposes of dealing with economic problems of practice, especially for the provision of medical care to indigent groups. These are useful and sometimes indispensable means for dealing with local problems that may be too small to be handled by a large county or state association, but all these developments should be made harmoniously if the public is not to be confused.

Hospital staffs also have meetings and develop educational programs for their members and for the physicians of the community. Here is the proper forum for presentation of clinical papers and case reports, which formerly contributed so largely to the programs of local societies. Again, specialists and many general practitioners are drawn to meetings of national and regional societies. All these programs, as a rule, are in the nature of postgraduate education, and have little to do with the economic, legislative or other activities that concern physicians most in their relations with the public. Great care must be taken that the county associations, which are the functional units of the medical profession, are not so starved that they do not perform the necessary social tasks expected of the profession. Perhaps the answer to this question is in the development of a stronger and better functioning state organization.

There is no doubt that the New England town meeting is one of the finest examples of democratic government. When, however, the town becomes too large, the town meeting has to give way to another form of government. The successful politician must remember that extraordinary effort is required to make up for the loss that the citizen feels when he no longer has his customary forum for making known his wants — the larger the organization, the more difficult it is to make up for this loss. These developments must take place without making the individual physician feel that he is remote from those who direct his affairs.

In spite of many distractions it has amazed me to see how much devoted service is given to organized medicine and to the mechanics of providing better facilities for physicians by the very men who are busiest. I have observed that the vast majority of so-called "medical politicians" have risen to their positions primarily because they are respected by

their fellows as physicians. My first impression on beginning my duties as a delegate was one of admiration for a system that brought to the top so many physicians of high quality. The exceptions are conspicuous indeed.

During the war the staff at the American Medical Association headquarters was greatly depleted, and we are not yet fully caught up with our back work. That was part of the price we paid for the war, and it is a contribution of which every physician can be proud. It was inevitable that contacts between state societies and the American Medical Association during this period should have been deficient, and it was inevitable that criticism came from individual physicians who in their remote posts about the world had ample time to think upon the wrongs of the world in general and organized medicine in particular. Most physicians on sober reflection, however, will understand the situation. I am glad to report that the staff is now being filled with competent men who, under the direction of the Board of Trustees, are pursuing a program to develop the responsibilities of the profession to the public and also to develop more intimate and frequent contacts with the members who carry on the burden of state and county activities.

One of the means developed to bring the Association closer to the individual member was the so-called "Grass Roots Conference" at Atlantic City, where county officers had a meeting of their own and a chance to discuss the problems that concerned them.

The American Medical Association is also assisting in the development of regional conferences attended by the responsible officers of the state societies in that particular region together with members of their important committees. I believe it was Dr. Fishbein who once said that the burden of organized medicine is carried by about 3000 physicians in the United States. These are the men who make up these conferences. Not only are there discussions of problems that are of interest to the members but also officials of the American Medical Association are present to report to them and to learn from them, for this is a two-way affair. In New England we have gone still farther, as you know, by the organization of the Council of the New England State Medical Societies. This council meets three or four times a year, and since it consists of only three or four delegates from each state society, it is small enough to come to grips with the problems that are of peculiar interest to us in New England.

The productive life of a state society as an organization is most often found in its strong and active committees. These committees interest themselves in medical-care plans, legislation, care for the chronically sick, cancer, public health and hospitals — subjects that vitally affect relations with the public.

I recommend the institution of a program that we have found effective, and one that immeasurably increases the vitality and significance of these committees. At present in Connecticut there is scarcely a board or commission that has to do with health or welfare on the state level to which there has not been added a carefully chosen member of the Society. This is effective not only in keeping the Society informed and in representing the Society's interest but also in revealing ways and means whereby organized physicians may exert necessary leadership in a field that it is their obligation to develop. Members of these commissions lend weight to the deliberations of their committees.

The late George Vincent once said in explaining why Denmark had such an excellent health situation: "In Denmark every health officer is a physician and every physician is a health officer." I firmly believe that that is a desirable aim for the medical profession in the United States. We must develop a keener appreciation of our position of public trust. We must accept even more fully the obligation that goes with the trust. This is easily understood by the physician who works alone or with a few others in a small community where he has intimate contact with his chief selectmen and with the overseer of the poor, the chief of police and so forth, and perhaps he may occupy the post as local health officer. It is difficult, however, for the physician who lives in a large city to sense his public responsibility. At best he must express himself vicariously by means of the officials of his medical society, but it is his duty to see that his society fulfills its obligation in this regard, and if young men at the beginning of their professional lives do not see the example of their elders, they too will develop habits of indifference.

I recommend for consideration the advantages of developing a student membership in the state society. We have done this in Connecticut and have found it productive of good will among the young physicians. Unfortunately, medical students are likely to hear much of the alleged advantages of socialization of medicine by physicians who themselves have not indulged in personal medical practice. On the other hand there are few opportunities for them to hear what organized medicine is doing and can do for society.

I know that you have no medical school, but some of your New Hampshire boys are studying medicine elsewhere and are going to come back to be future members of this society, and you have interns and residents in your hospitals. I suggest that you concern yourselves with what they are thinking. Find out who they are and where they are studying and let them know that your society is interested in their welfare. Our student members, who now number 350, are very grateful for the copies of the *Connecticut State Medical Journal* that we send them.

The following arrangement has been found productive in Connecticut. About six years ago the

Connecticut Medical Examining Board, members of which are appointed by the Governor on nomination by the state society, foresaw the advantages of a close alliance between the Society and the Board, and as a result the executive secretary of the Society became the secretary of the Examining Board. This arrangement provided full-time administration for the Board as well as for the Society, and every prospective candidate for medical licensure came to the Society's office for his first contact. Dr. Barker, in his annual report to the Connecticut House of Delegates, made the following statement:

The good effect of this system cannot be measured. Most of the candidates come to the office for interviews and information and it is a surprising but none the less true observation that these physicians newly come to our state are more familiar with the activities and services of the Society's office than are many members of the House of Delegates. It is common for these candidates to ask even before they are settled here how they may become members of the Society either by transfer or election. All this is a privilege and an advantage that I believe no other state society enjoys and is the outcome of far sighted planning.

The advantages of this relation were even more apparent during the war when the executive secretary, Dr. Barker, was also the state chairman for the Procurement and Assignment Service. The result has been that the files in the office of the Society are not only complete but also official. We plan to have our physicians with us from the cradle to the grave.

Most of us, I believe, are out of sympathy with those who criticize national foreign policy before foreign audiences, and most physicians have little regard for would-be medical statesmen who attempt to bring pressure on organized medicine by arguing their ideas before lay audiences. With rare exceptions these dissident physicians have not participated as active members in the ordinary work of medical societies. They have rarely presented their arguments successfully before the organizations of medicine, and few of them have ever practiced individual medicine, which they so freely criticize. A reasonable opportunity should be given such persons to present their ideas before medical societies and to subject themselves to the discussion of the facts of life of medicine. I am sure that it would do them good.

What about the "lone-wolf" member who never comes to medical meetings? What about the occasional member who stays within the letter of the law, overcharges the poor and skates on the thin ice of professional respectability? I am sure that such members are few in number, but one bad apple has an effect on the whole barrel, and the adverse publicity caused by one unscrupulous physician brings the whole profession into disrepute. Some laymen believe that this is the most important item on the medical society's agenda. They point to the reluctance of physicians to bring to book a fellow member. This reluctance, they say, gives relative immunity to this sort of racketeer. The layman

points out that disciplinary action can be undertaken effectively only by the medical profession itself and that the legal profession has devised a powerful grievance committee to process complaints of unprofessional conduct against any lawyer. He will often add that the committee is not called on as often as he would like to have it, but it is there and no lawyer relishes a summons to appear before it, perhaps the grievance committee was devised because a lawyer on being admitted to the bar becomes an officer of the court, and since the court is sensitive to any unprofessional action, the bar association itself undertakes to discipline its own members.

Medical-insurance plans have extended their benefits widely as in New Hampshire and many other states. There develops a need for handling complaints that may originate with the medical-insurance administration, with the individual physician or with the individual patient. Every so often the "lone wolf" has to be trapped and has to be tamed. I am told that the grievance-committee mechanism works well when it is set up and used, and the very fact that it is there has a restraining influence.

When plans for prepaid medical service in Connecticut were being discussed, I pointed with pride to the experience in New Hampshire with the indemnity type of contract and, explained that, although there was no written agreement, the indemnity payments actually constituted a fee table for the indigent — that is, a gentleman's agreement that the table would be sufficient without further

charges when the family income is low. One of our cynical businessmen remarked that such an arrangement might work well in New Hampshire but not in Connecticut. I granted the New Hampshire part of the statement but was inclined to resent the implication that Connecticut waters were infested with sharks, until he told us of a man in his employ whom the physician charged inappropriately considering his reduced circumstances. I am a good organization man and I shall always defend another physician so long as I am convinced of his integrity and fair dealing, but I deeply resent actions that give physicians a bad name by causing hardship to a poor patient and I therefore recognize that proper policing of our own membership is one of our major responsibilities. This is a job that must be done with fairness and firmness, and with rare wisdom, and it is a job that falls naturally on the shoulders of the elders. I am glad to talk freely about self-discipline before a state society that needs it less than any I know, but I do not doubt that even you will have some experiences with shark fishing.

The ten-point health program of the American Medical Association is a fine statement of practical idealism. Parts of this program are already being put in motion by organized effort, but like the Ten Commandments many elements of the program depend upon personal integrity in the daily life of every physician. Effective public relations come from within. Our own members are our first public.

179 Allen Street

## POSTARSENICAL ENCEPHALOPATHY IN THE TREATMENT OF SYPHILIS IN WOMEN\*

S CHARLES KASDON, M D,† AND MORRIS W SHAPIRO, M D ‡

BOSTON

AT LEAST 60 per cent of adults receiving arsenical antisyphilitic therapy who develop postarsenical encephalopathy are pregnant women. The mortality in this most serious complication in the treatment of syphilis approaches 70 per cent. Postarsenical encephalopathy, the term considered most apt, has also been described under the following titles: cerebral purpura, serous apoplexy, hemorrhagic encephalitis, pericapillary encephalorrhagia, medullary perivascular necrosis and toxic encephalitis.

There is a widespread lack of familiarity with this cause of death in 13 per cent of the total number of patients treated by the massive five-day arsenical

course.<sup>1</sup> Postarsenical encephalopathy was the cause of 95 per cent of 211 maternal deaths in Arnell and Guerriero's<sup>2</sup> series, 27 per cent of maternal deaths in Kennedy and Hennington's<sup>3</sup> group and 8 deaths in five years at the University of Iowa clinics.<sup>4</sup>

This paper reports 2 fatal cases of postarsenical encephalopathy, 1 in pregnancy, with autopsy findings in both, and also presents several new factors in its management. These new developments are important in spite of the recent advent of penicillin therapy for syphilis, since there is little question that many patients receiving antisyphilitic therapy will be dependent upon arsenicals for some time to come.

### SYMPTOMS

The clinical picture that is characteristic of this syndrome is most conveniently described by a noso-

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‡Instructor in pathology and bacteriology, Tufts College Medical School, pathologist, Carney Hospital.

graph suggested by Kühnel.<sup>4</sup> The patient is a young woman, usually pregnant, and generally with a past history of good health except for the presence of syphilitic infection. The disease is often of fairly recent origin or, in any case, manifest by recent signs of active infection. It may, however, be a latent infection, generally untreated previously and with very little evidence of syphilis except for the positive serologic findings. Antisyphilitic treatment is begun in the last trimester of pregnancy with arsphenamine or one of its related drugs, with two to four injections of average dose, and the patient may lack symptoms for two to five days. Many patients have transitory but intensely significant complaints, such as slight headaches, nausea or vomiting, or both general indisposition, restlessness and, rarely, a rapidly fading exanthem, after which there is a rather sudden onset of headache, dizziness, malaise, nausea and vomiting with a moderate leukocytosis. Within twenty-four hours marked restlessness ensues, with mental confusion followed by an irregular number of convulsions and coma. At this stage the patient is taken to the hospital with a diagnosis of eclampsia. Later — from a few hours to one day — irritative cerebral symptoms become more pronounced, including trismus, tetany, accentuated reflexes, a positive Babinski sign and the irregular respiratory phase of Cheyne-Stokes type. Death follows deepening coma. In most cases death occurs three to five days after the acute onset.

#### INCIDENCE

It was scarcely two years after the introduction of arsphenamine in the treatment of syphilis by Ehrlich when hemorrhagic encephalitis as a toxic manifestation of this therapy was reported.<sup>6-8</sup> The literature since that time has had many reports dealing with the most frequent cause of death in the treatment of syphilis.<sup>10</sup> Glaser, Imerman and Imerman<sup>11</sup> (1935) reviewed the literature and culled 155 cases, adding 3 of their own. Smith and Newbill<sup>12</sup> found 17 more to report by 1939. Since that time a review of the literature available from 1939 to 1946 has offered 88 new cases.<sup>13-16</sup>

The incidence of arsenical encephalopathy in patients treated for syphilis by the multiple-course method is variously quoted as 1,2500 cases,<sup>17</sup> 1:6500<sup>11, 14</sup> and 1:2000.<sup>18</sup> That arsenical encephalopathy occurred with greatest frequency in pregnancy has only recently been appreciated. In 36 reported cases of encephalopathy in adult women studied in the literature from 1939 to 1946, 27 (75 per cent) were pregnant. This shows close agreement with the incidence during pregnancy of post-arsenical encephalopathy in the reports of Ingraham<sup>19</sup> (64.3 per cent), Meirovsky and Kretzmer<sup>11</sup> (60 per cent), Cormia<sup>12</sup> (80 per cent) and Paley and Plehette<sup>10</sup> (70 per cent). Arnell and Guerriero<sup>2</sup> reported that fatal arsenical encephalopathy is four

times more frequent in pregnant than in nonpregnant women.<sup>20-21</sup>

In spite of the wealth of evidence that the treatment of syphilis in pregnant women should be undertaken with grave circumspection and only when clearly indicated, conflicting views still exist in the attitude of syphilologists and even more so in the minds of obstetricians, upon whom the responsibility for treatment rests primarily. For it is the obstetrician who almost universally discovers the presence of syphilis in pregnant women and must decide whether treatment is warranted or not. Some writers convey the impression that pregnant women with syphilis tolerate arsenical therapy well.<sup>22-24</sup> However the general consensus contradicts this attitude. The most acceptable impression, as stated by Plass and Woods,<sup>4</sup> is that "a pregnant woman is probably more susceptible to the deleterious as well as the beneficial effects of modern arsenical therapy."

#### PATHOGENESIS AND ETIOLOGY

That typical lesions are not entirely dependent upon arsenicals has been demonstrated by reports of cases in which no arsenic has been administered.<sup>25-28</sup> The overwhelming number, nevertheless, follow the use of pentavalent arsenic.<sup>29</sup> An unusually high frequency has been noted after the administration of sulfarsphenamine,<sup>31-33</sup> resulting in almost complete condemnation of its use.

Mapharsen is now employed almost universally in the massive five-day course<sup>34</sup> and other accelerated arsenical courses in the treatment of syphilis, but the incidence of severe central-nervous-system reactions remains at 1 per cent or more and the mortality from complications of therapy at 0.3 per cent.<sup>31</sup> It is obvious that when this relatively high incidence of severe toxic reactions in the accelerated arsenical therapy of syphilis is considered together with the increased susceptibility of patients with ante-partum syphilis, the cautious therapist should hesitate to subject his pregnant patients to the dangers of encephalopathy.

A clear statement of the mode of action whereby arsphenamine therapy results in encephalopathy was presented by Ehrlich<sup>35</sup> in 1914. He concluded that the mechanism was first a dilatation of the cerebral vessels followed by edema and perivascular hemorrhage. More recent studies<sup>36-38</sup> cling to this basic theory of development. Deficiency of vitamin C<sup>39</sup> and P<sup>40</sup> may play a part, but the production of typical lesions in the brain of normal rabbits with an adequate vitamin intake<sup>41-43</sup> throws doubt on these factors. The theory of the relation between nitritoid crises and vascular damage leading to cerebral edema is open to the objection that nitritoid crises have yet to be demonstrated in Mapharsen therapy.<sup>37</sup> Selzberger<sup>44</sup> and later Moriyama,<sup>45</sup> using patients' serum, were able to transfer arsenic sensitivity to guinea pigs. Landsteiner and Jacobs<sup>46</sup> demonstrated arsenic anaphylaxis in guinea

pigs. However, Gjessing<sup>70</sup> questioned whether arsenic sensitivity was the cause of the encephalopathy, since he reported a patient who recovered from typical clinical postarsenical encephalopathy and who received treatment with neoarsphenamine six weeks later with no untoward results. Klaften<sup>44</sup> corroborated this finding. In addition, a large number of cases have followed only one known arsenical injection. Tzanck and Lewis<sup>43</sup> rule out the Herxheimer augmentation of the virulence of the spirochete through treatment employed to combat it, since hemorrhagic encephalopathy has been too widely reported in nonsyphilitic patients. Osterberg and Kernohan<sup>71</sup> found arsenic in relatively large amounts in the brain analysis in doubtful diagnostic problems, as did Gierlich and Kunkle.<sup>72</sup>

The explanations offered for the especially increased incidence of postarsenical encephalopathy in pregnancy are likewise many.<sup>73</sup> Arnell and Guerriero<sup>2</sup> believed that the increased incidence in pregnancy was explained by the greater storage of arsenic in the placenta that had been demonstrated by Eastman and Dippel.<sup>74</sup> This was gradually set free in the blood over a period of several days, thus increasing the circulating amount of arsenic. Pregnancy presumably produces a degree of capillary alteration that is further aggravated by the action of arsenic on the capillaries, resulting in the toxic phenomena.<sup>46, 75</sup> Excessive protein deficiency in pregnancy suggested as a predisposing cause is not conclusive, since many have noted that a large number of women with ante-partum syphilis and many with marked debility and toxemia have been treated with arsenic without a noticeable increase in the development of encephalopathy in this group.

#### TREATMENT

The management of acute postarsenical encephalopathy in pregnancy can best be approached from the prophylactic or preventive standpoint, secondly, the major principles of treatment and thirdly, the specific agents that are of value in the management of the acute toxic state.

Preliminary treatment with bismuth or mercury compounds has no effect whatsoever in preventing encephalopathy during gestation. The dosage level of the arsenical used is also of undetermined importance,<sup>12</sup> since many cases follow very small quantities of arsenic. The undeniable increase in frequency of this complication during the massive five-day course of arsenical treatment in syphilis tends to direct more interest toward the amount of arsenical administered. It is therefore believed that minimal dosage levels are to be preferred. The essential fact that positive and unequivocal evidence of syphilis in pregnancy must be obtained before arsenical therapy is undertaken deserves great stress. In the light of modern opinion, ante-partum treatment with arsenic for syphilis is not necessary when adequate therapy has already been administered.

The concept that patients in the last trimester of pregnancy are more susceptible to encephalopathy is probably due to the fact that in the past the greatest number of patients were not seen by the physician until late in pregnancy. Actually, encephalopathy has been described in all but the first month of gestation. In the series of 50 cases collected from the literature of the past ten years the average duration of pregnancy was five and four-fifths months. It is certainly likely that the date of onset of treatment is more important than the "metabolic overload" that occurs at the end of pregnancy. It is also certain that the arsenical treatment of pregnant women who have a history of sensitivity to arsenic or other metals is at best hazardous. Penicillin is unquestionably the drug of choice, since encephalopathic changes have yet to be reported in the treatment of syphilis with penicillin.

The major principle of treatment for this toxic reaction is also clear. There is little question that therapy is more effective if instituted before the onset of coma and convulsions. It is possible to start treatment before the severe symptoms develop, since the prodromal signs of slight headache, nausea or vomiting, or both, generalized indisposition, restlessness and the relatively infrequent exanthem usually precede the onset of convulsions and coma by one or two days. If the physician is aware of these significant but mild signs of warning following the administration of arsenicals the prompt institution of adequate treatment before coma and convulsions ensue is at present the only means of reducing the mortality from this complication in the treatment of syphilis with arsenicals.

The intramuscular administration of adrenalin hydrochloride in a 1:1000 solution in repeated dosage has long been in favor. The rationale for its use has been presented above, but in spite of the proclaimed specificity of adrenalin-like substances, the mortality has remained high. Much stress has been placed on the thiosulfates in the treatment of arsenical toxicity, but it is generally admitted that their action has a very slight and definitely questionable value. The long list of additional drugs and vitamins that have been used, such as sodium dehydrocholate, calcium chloride, numerous sedatives, magnesium sulfate, components of the vitamin B complex, acetylcholine, vitamin K, vitamin C and vitamin P, has not appreciably altered the course of the disease. Perhaps as great stress has been placed on reducing the tendency to cerebral edema by means of hypertonic solutions and especially by spinal-fluid drainage. In fact, Ransome et al.<sup>1</sup> kept all their patients in the erect sitting position throughout the whole course of treatment and reported no mortality in the 5 cases studied. Their explanation for the effectiveness of this technic is fallacious since the reduction of cerebrospinal-fluid pressure and cephalic venous pressure, which they claim as the cause of improvement, can at best

have been very transitory. In view of their reported results, however, additional evidence for the efficacy of the postural treatment is awaited.

Much more important is the newly introduced drug BAL (2,3-dimercaptopropanol),<sup>76-78</sup> a specific detoxifying agent for arsenic, mercury, gold and other heavy metals when injected intramuscularly or intravenously. The antidotal action of BAL is due to its ability to remove arsenicals from combination with the tissue-cell proteins with the excretion of a stable and relatively nontoxic substance. The dosage of BAL (10 per cent solution in peanut oil with 20 per cent benzyl benzoate) is 2.5 to 5 mg per kilogram of body weight, injected four times daily at four-hour intervals the first two days and then twice daily thereafter for six or more days. The maximum tolerated divided dose in rabbits is 100 mg per kilogram of body weight. The major reactions to BAL are "constriction in the throat," preternal oppression, burning of the lips, lacrimation, dryness of the mouth, local tenderness at the site of injection, nervousness, restlessness, nausea and vomiting. No severe toxic reactions have thus far been reported.<sup>79</sup> Eagle and Magnuson<sup>78</sup> presented 55 cases of postarsenical encephalopathy out of 227 toxic reactions to antisyphilitic therapy that were treated adequately with BAL. Of these, 24 patients developed coma or convulsions, or both, with a mortality of 25 per cent, when treated within six hours of the onset of symptoms. Those treated later than six hours after the onset of symptoms had a mortality of 45 per cent. In 15 mild cases, there was 100 per cent survival. The authors report an over-all reduction of mortality from 70 per cent to 11 per cent by the use of BAL. It promises to be of the greatest value in the management of the most severe toxic reactions to arsenic. A high-protein, high-carbohydrate and low-fat diet is advisable as well.

### CASE REPORTS

Two young women with asymptomatic syphilis came to post-mortem examination after neosarphenamine treatment. These therapeutic deaths occurred within a six-month period. One of these women was pregnant.

**CASE 1\*** V W (C. H. A-42-44) a 34-year-old woman became pregnant for the first time after treatment for infertility. She was 2½ months pregnant when first seen. The past history and family histories were completely irrelevant and examination at that time revealed no abnormalities of moment. A routine specimen submitted for examination showed a positive blood Hinton test. This was repeated, as well as a Wasserman test and all reports were returned strongly positive. Blood examination, physical examination and a careful review of the husband's history failed to reveal any evidence of syphilis to him. Routine premarital blood examination 2 years earlier had been reported negative. The patient was referred to a competent syphilologist for further diagnosis and suggestions for management. She received 0.2 gm of bismuth at weekly intervals for 6 weeks without reaction and then was started on neosarphenamine. The first dose of 0.3 gm was given 10 days and the second

dose 3 days before admission. On the day she received the second dose of neosarphenamine she also made a routine visit to her obstetrician who found a blood pressure of 100/70; the urine contained no albumin, and there were no toxic signs or symptoms. For the next 2 days the patient had headaches, epigastric distress, unusual restlessness, massive gaseous eructations, chilly sensations and no bowel movements. On the 3rd morning she was found lying in bed in a semicomatose state with frequent bouts of stertorous breathing, repeated extensor tonic convulsions at intervals of 5 to 8 minutes, excessive salivation and moderate generalized cramps. The convulsions lasted about 40 to 60 seconds; the patient remaining semicomatose between seizures. The physician who was called in to see her believed that she was suffering



FIGURE 1 Coronal Section through Cerebral Hemispheres (Case 1)

Note symmetrical distribution of petechial hemorrhages, confluent in areas and confined for the most part to the white matter. The corpus callosum and the internal capsule show marked involvement.

from eclampsia, and the patient was admitted to the hospital on October 19, 1942.

Physical examination revealed an acutely and seriously ill woman, who was having convulsions lasting 1 or 2 minutes and occurring every 5 to 8 minutes with extensor spasm of both arms and legs, a moderate degree of opisthotonus, stertorous breathing, excessive salivation and moderately severe cyanosis. She did not respond to commands. The deep reflexes were hyperactive and the Babinski reflexes extensor in nature.

The temperature was 98.6 F, the pulse 96 and the respirations 36; the blood pressure was 84/50.

Examination of the blood disclosed a red-cell count of 3,520,000 with a hemoglobin of 78 per cent, and a white-cell count of 20,800 with 90 per cent neutrophils, 6 per cent lymphocytes, 2 per cent monocytes and 2 per cent band forms. The blood Hinton reaction was ++++. The nonprotein nitrogen was 22.4 mg per 100 cc. Blood culture showed no growth. Urinalysis was negative.

The convulsions were controlled with 0.016 gm of morphine sulfate and 0.2 gm sodium luminal intravenously. A total of 500 cc. of 10 per cent glucose in water was given intravenously.

A lumbar puncture was performed and the spinal fluid findings were as follows: 101 white cells and 107 red cells per cubic millimeter, a total protein of 300 mg, and a sugar of 51 mg per 100 cc. and a chloride of 900 milliequivalents per liter. A direct smear revealed 60 per cent polymorphonuclear leukocytes and 40 per cent lymphocytes, no organisms were seen. The spinal fluid Wasserman reaction was negative.

The diagnosis was toxic encephalopathy of undetermined nature following arsenical therapy. In spite of the control of convulsions by adequate sedation the patient's course was rapidly downhill and she expired 22 hours after admission.

\*Reprinted through the courtesy of Dr. L. E. Phaneuf.

At post-mortem examination, which was performed 2½ hours after death, the outstanding gross findings were seen in the brain, which was heavy and weighed 1525 gm. There was no epidural or subdural hemorrhage. The pia-arachnoid was transparent, and its vessels were congested. It was hemorrhagic over the pons and the medulla. Multiple sections revealed innumerable capillary hemorrhages, confluent in areas, symmetrically distributed throughout the white

CASE 2\* H G, a 31-year-old woman was known to have had syphilis for the past 10 years. She had one child 9 years old, who was living and well. Because of a persistently posi-

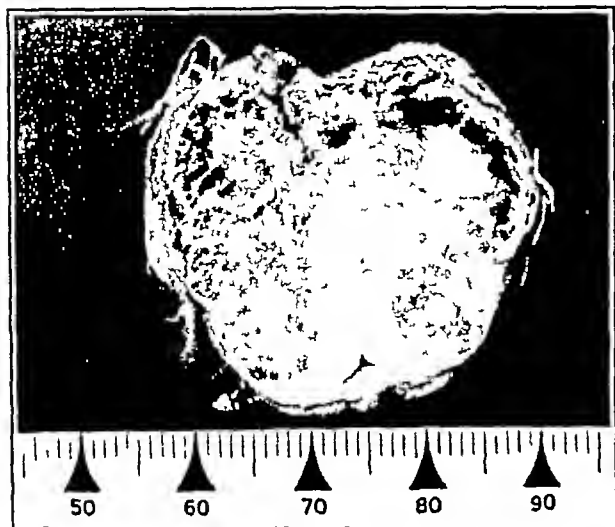


FIGURE 2 Section through Pons (Case 1)  
No confluent areas of hemorrhage, with softening

matter of the brain. Softening and necrosis was most marked in the pons, medulla, cerebral peduncles, the corpus callosum, and the internal and external capsules (Fig 1 and 2). The vessels throughout were congested, and the cut surface was moist. The ventricular system was intact and regular and contained cloudy cerebrospinal fluid. The cervical cord was free of disease.

The remainder of the organs of the body showed severe congestive changes, the typical findings of pregnancy and ter-

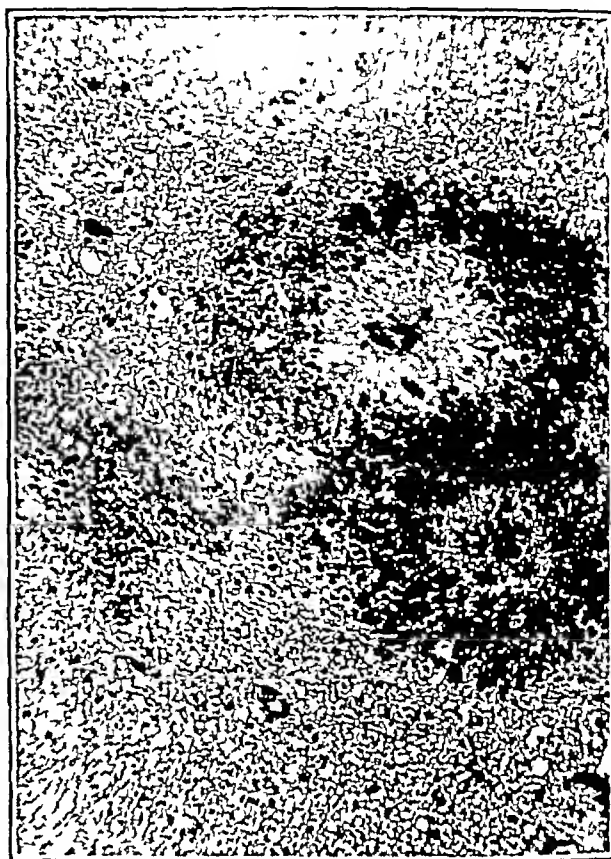


FIGURE 3 High-Power Photomicrograph (Case 2), Showing Hemorrhages of the Ring-and-Ball Types with Fibrin Thrombi in the Lumens of the Blood Vessels

tive blood Hinton test, she was started on treatment for tertiary asymptomatic syphilis at the Outpatient Department on August 1, 1941 (Table 1). On April 15, 1943 (15

TABLE 1 Treatment Given in Case 2

TREATMENT	DOSE	PERIOD OF THERAPY	BLOOD HINTON REACTION	TOXIC REACTION
Bismuth salicylate*	100 mg	8/1/41-11/1/41	Positive	None
Mapharsen*	0.05 gm	11/7/41-2/5/42	Positive	None
Bismuth salicylate*	100 mg	2/20/42-6/5/42	Positive	None
Mapharsen	0.06 gm	6/12/42	Positive	None
Neoarsphenamine	0.25 gm	6/16/42	—	None
Neoarsphenamine	0.45 gm	6/23/42	Doubtful	None
Bismuth salicylate*	100 mg	6/23/42-Dec 42	Doubtful	None
Neoarsphenamine*	0.25-0.45 gm	1/6/43-3/31/43	Negative	Toxic encephalopathy (April 15, 1943)

\*Given each week for period indicated.

минаl cardiac failure. There was severe passive congestion and central necrosis in the liver.

Microscopically, the brain showed two basic lesions: punctate and ring hemorrhages, with injury of the capillary walls, and often secondary mural and obstructing thrombosis. In areas there was beginning secondary infarction of the brain tissue.

The second case, although not that of a pregnant woman, is included because of its similarity to the first in other respects.

days after the last dose of neoarsphenamine), she suffered the sudden onset of severe headaches followed in 6 hours by tonic convulsions and loss of consciousness. She was admitted to the hospital on April 15. At that time the extremities were spastic and the reflexes hyperactive, and she was in a comatose state. The temperature was 98°F, the pulse 88, and the respirations 16. The blood pressure was 140/70. The white-cell count was 13,500, and the red-cell count was 4,150,000. The urine was negative for albumin and sugar. The blood nonprotein nitrogen was 25 mg per 100 cc. A

\*Cambridge City Hospital Case A-43 20



lumbar puncture revealed clear spinal fluid under increased pressure. There were no cells present. The total protein was 56 mg per 100 cc. The gold-sol curve was 0000000000.

The patient died on the following day.

A post mortem examination limited to the head was performed 2 hours and 20 minutes after death. The brain weighed 1250 gm. The white matter of the corpus callosum the subcortical white matter of the hemispheres and the white matter of both internal capsules were riddled with innumerable fresh capillary hemorrhages. There were capillary hemorrhages into the ependyma of the lateral ventricles, with slightly blood tinged fluid in the lateral ventricles. These hemorrhages were symmetrically distributed. The cerebral peduncles, the pons the medulla and the cervical cord were free of disease. Microscopically the brain showed two basic lesions punctionate and ring hemorrhages with injury of the capillary walls, and often secondary mural and obstructing thrombosis (Fig 3) and thrombosis of the capillaries without hemorrhage, but with beginning secondary infarction of brain tissue.

It appeared that as a result of changes in the vessel wall hemorrhages or thrombosis or both resulted. The dura showed vascular changes, with bleeding similar to those in the brain.

### Discussion

Postarsenical encephalopathy due to neoarsphenamine is a well recognized clinical and pathologic entity. The disease is infrequent, occurring in about 1-6500 cases treated, and generally runs a rapidly fatal course, although recoveries have been reported in the literature. The average time of onset of symptoms after the last injection of neoarsphenamine is about two and a half days. In the cases reported above it was three days in Case 1 and fifteen days in Case 2. The usual number of injections previous to the onset of symptoms is two or three. In Case 1 it was two, and in Case 2 it was twenty-three injections.

Case 1 was in all respects typical of cases observed during pregnancy. The disease usually occurs during the last trimester of pregnancy in patients showing asymptomatic syphilis discovered on serologic examination. The onset early in the first course of injections of neoarsphenamine is common.

The convulsions occurring in the last trimester of pregnancy naturally bring forth a diagnosis of eclampsia on the part of the physician. However, the following differential points are present: a positive history of arsenical treatment, usually within three days, no hypertension, no albuminuria, no edema, and no toxic symptoms. The course is rapidly downhill, death occurring in two or three days in 70 per cent of cases until the advent of BAL as a specific detoxifying agent for arsenic.

The lesions in the brain in Case 1 were very extensive and involved the vital medulla. The liver cells also showed destructive changes, a rather unusual finding in postarsenical encephalopathy.

Case 2 was less typical so far as the number of injections and the time elapsing from last injection to onset of symptoms are concerned. The course of the disease and the autopsy findings were quite typical. The pathologic changes in the brain consisted of swelling of the endothelial cells of the capillaries,

congestion of vessels and edema of the brain, punctate and ring hemorrhages symmetrically distributed, thrombosis of the capillaries (fibrin thrombi), and infarction of brain tissue.

The pathogenesis of this disease is not entirely clear. Many theories have been offered to explain it. It appears, however, that the arsenicals are responsible in setting off a series of events that frequently culminate in the death of the patient. The first is definite damage to the walls of the capillaries, which is followed by hemorrhage of the ball-and-ring type and by thrombosis. Subsequently, the brain areas involved undergo infarction, with necrosis of brain tissue. The damage to the vessel walls is thought to be on the basis of allergy or sensitivity, in some manner greatly accentuated during pregnancy.

For the treatment to be effective, this condition must be recognized in the first few hours after the onset, and treatment promptly started. Therapy should include sedation and, most important of all, adequate and early administration of BAL, adequate treatment succeeds in lowering the over-all mortality rate from 70 to 11 per cent. The single most essential fact in control of this serious complication of syphilitic treatment with arsenicals is the application of therapy before the onset of coma and convulsions. It is possible to start treatment sufficiently early if one is aware of the prodromal symptoms that precede the onset of coma and convulsions. The most significant symptoms are headache, epigastric distress, restlessness and nausea or vomiting, or both. The use of penicillin as the drug of choice in the treatment of syphilis during pregnancy may prove to eliminate encephalopathy entirely and is therefore recommended. The use of intravenous arsenicals during pregnancy for any disease but syphilis should be condemned. Similarly, the diagnosis of syphilis should be unequivocally established and treatment clearly indicated before arsenical therapy is undertaken. The specific detoxifying agent for arsenic, BAL, deserves a wide use in the control of this complication.

### SUMMARY

The cases of 2 young women with asymptomatic syphilis who came to postmortem study after neoarsphenamine treatment are presented. These deaths due to therapy occurred within a six-month period. One of these women was pregnant and near term.

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## MENINGOCOCCAL PNEUMONIA\*

## Report of Two Cases with Meningococcal Effusion in One

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WITHIN a period of a month in 1942, 2 cases of pneumonia in which the meningococcus was implicated, without meningeal involvement, were observed. It has been known for some time that extrameningeal meningococcal infections are not uncommon,<sup>1</sup> but the attention directed to the respiratory phase of such infections is very scant. In view of the uniqueness of one of the cases observed and because of the lack of recent literature on the subject, it seemed worth while to report the cases and briefly to review the literature. The fact that most of the cases previously reported involved military personnel in World War I also affords an opportunity to review similar experience in World War II.

## CASE REPORTS

P. C. (B.C.H. 1088509), a 56-year-old man entered the hospital on November 24, 1942, because of chills and fever, cough and vague chest pain of 4 days duration. Physical examination revealed moist rales in the right axilla and a roentgenogram on the day of admission was reported as showing pneumonia of the right middle lobe. A blood culture taken before exhibition of sulfadiazine revealed a growth of Type 1 meningococcus. Neufeld typing of the sputum was reported as negative.

On sulfadiazine therapy from November 24 to 30 the patient made an uneventful recovery. A repeat x-ray film on December 3 was reported as being within normal limits. The white-cell count dropped from 14,100 on entry to 9150. Blood cultures on November 29 and December 7 revealed no growth and the patient was discharged on December 10.

In this case of pneumonia routine blood cultures showed a growth of Type 1 meningococcus. Since Neufeld typing of the sputum was negative for both the pneumococcus and the meningococcus the evidence that the pneumonia was meningococcal in origin is indirect but warrants attention. The response to sulfadiazine was characteristic of that expected in either pneumococcal or meningococcal infections and did not resemble the response of pneumonias of virus etiology.

L. L. (B.C.H. Case 1090910)† a 53-year-old baker's helper was admitted to the hospital on December 21, 1942 with complaints of pain in the left side of the chest of 3 days duration, hemoptysis of 3 days duration and rash on the legs of 1 day's duration. For the past 2 weeks the patient had had a "heavy" cough and had expectorated slight amounts of mucoid sputum, which was occasionally blood streaked. "Nearly" not feeling too well, he had been able to work "nearly" every day. However 3 days prior to admission he noticed a sharp pain in the left midaxillary region accentuated on deep breathing and coughing. Expectoration of

thick rusty sputum was noted on the same day. The symptoms became increasingly severe. On the day before admission a chill and fever were noted, and for the first time a red rash was seen on both lower extremities. The skin lesions were not painful, itchy or raised above the skin surface. The patient denied any previous similar manifestations.

The patient was unmarried and had been on relief for many years. He was a known chronic alcoholic of many years' standing. At the age of 20 he had had a penile sore and had been told that he had "had blood" many years before the present episode.

In January 1938 he had been seen in the Outpatient Department for shortness of breath. A positive blood Hinton test was noted. Physical examination showed an aortic diastolic murmur and the diagnoses of late latent syphilis, syphilitic heart disease with aortic regurgitation and generalized arteriosclerosis were entered in the record. A foot roentgenogram of the chest revealed widening of the ascending and descending aorta, raising the question of aortic aneurysm. After a few intramuscular injections of bismuth oil had been given the patient absented himself from the clinic.

Physical examination disclosed a markedly dyspneic poorly nourished man who grunted with every respiration. The face was flushed and dilatation of the aortic aorta was noted. Over the thighs, feet and legs there was a petechial rash the lesions being pin-point to 3 mm. in diameter, some were discrete and others confluent and did not blanch on pressure. The teeth were in very poor condition but the gums were firm and no bleeding was noted. The neck was supple and hernial and Brudzinski's signs were absent. Examination of the chest revealed limitation of respiratory excursions of the left hemithorax. Decreased tactile fremitus, marked diminution of breath and voice sounds and dullness on percussion were noted over the lower half of the left portion of the chest, extending up to the level of the third rib anteriorly and the fifth thoracic vertebra posteriorly. The trachea was deviated to the right. The apical impulse was not made out on palpation; there was sinus rhythm with a rate of 100 per minute, and an aortic diastolic murmur was heard best in the third left interspace. Neurologic examination was not remarkable. The patient was somewhat incoherent and confused but cooperative and euphoric.

The temperature was 101.8°F the pulse 118 and the respirations 34. The blood pressure was 130/100.

Examination of the blood demonstrated 11.0 gm. of hemoglobin and a white-cell count of 8950 with 84 per cent neutrophils and 17 per cent lymphocytes. The hematocrit was 36 per cent and the corrected erythrocyte sedimentation rate 35 mm. in 1 hour.

The sputum was thick, rusty and tenacious. Gram's stain revealed the sputum to be loaded with gram negative diplococci; the polymorphonuclear cells burst with these gram negative diplococci which had the morphology of meningococci. A number of gram positive diplococci outside the polymorphonuclear cells were also noted. Neufeld typing and culture revealed predominantly Type 1 meningococci with some Type 15 pneumococci.

A roentgenogram confirmed the impression that fluid was present in the left side of the chest. Thoracentesis was productive of 1250 cc. of serosanguineous fluid which contained 4500 leukocytes per cubic millimeter, 95 per cent of which were polymorphonuclear cells. Culture of this chest fluid on blood agar plates was positive for gram negative diplococci which were typed as Type 1 meningococci.

Blood cultures on admission before institution of chemotherapy and on the 3rd and 13th hospital days were negative for the meningococcus. Urinalyses were not remarkable and there was a positive blood Hinton test but negative spinal fluid Hinton and Wassermann tests. The spinal fluid examinations including culture were not remarkable.

\*From the Fifth and Sixth Medical Services (Boston University) Boston City Hospital.

†Instructor in medicine, Department of Medicine, Georgetown University School of Medicine; formerly resident, Fifth and Sixth Medical Services, Boston City Hospital.

†The bacteriologic studies in this case were made in the laboratory of Dr. Maxwell Finland, at the Thorndike Memorial Laboratory, Boston City Hospital.

ture The operation results in incomplete removal of the gland and recurrent obstruction

Believing that these operative procedures were far from satisfactory, Millin studied, on cadavers, a new approach to the prostate. He was convinced that since the prostate is essentially an extravescical organ, it should be removed by an extravescical approach. As a result of his studies the retropubic operation was devised.

*Preoperative preparation* The usual studies of renal and cardiovascular function are made before operation. Intravenous pyelograms are obtained. The patient is not catheterized unless there is urinary infection that fails to respond to treatment or unless renal function is poor. Urethral-catheter drainage is avoided if possible.

*Anesthesia* Low spinal anesthesia or Pentothal Sodium and nitrous oxide and oxygen are used. The patient is cystoscoped for the first time on the operating table.

*Operative technic* The bladder is exposed by a mid-line suprapubic incision. The prevesical space is opened and cleared of fat. A specially devised self-retaining retractor separates the rectus muscles and presses the bladder upward. The veins on the anterior and lateral aspects of the prostate are exposed and carefully studied, since their distribution varies considerably. These veins are situated in the prevesical layer of the pelvic fascia. A large central vein arises from the deep dorsal vein of the penis, other veins lie on each side. These veins are tied with the aid of a boomerang needle. The prostatic capsule is opened transversely, and bleeding points are grasped between toothed forceps. The incision is then carried down to the adenoma. The apex of the prostatic mass is freed from the capsule, and the dissection is continued up to the bladder neck. Here the prostate is freed by sharp dissection. Bleeding points are controlled by ligature or electrocoagulation. After removal of the hypertrophied gland a No. 18 catheter is passed through the urethra to the bladder. The prostatic capsule is closed with interrupted sutures. The abdominal wound is closed, a small drain being left in the prevesical space.

In his first 20 cases Millin reported no mortality and few postoperative complications. Since this first report Millin has performed over 400 retropubic prostatectomies, which he described at the July, 1947, meeting of the American Urological Association in Buffalo, New York. The mortality was approximately 4 per cent. Millin's enthusiasm for the procedure was unbounded. In his book describing the operation, he states that the extravescical retropubic approach to the prostate enables one to deal with all pathologic conditions within that organ and its contained urethra.<sup>3</sup>

Among the audience who listened to Millin's presentation, there were a few skeptics, consisting of some who had seen Millin operate and who had

performed retropubic prostatectomies themselves. Their enthusiasm seemed to be less than Millin's, tempered no doubt by their own experiences. The prevailing opinion, however, was one of considerable interest and an eagerness to go home and "try it out."

Since then little has appeared in our own literature concerning this new method of removing the prostate, although the few reports available have been favorable.

The recent French literature includes a description of retropubic prostatectomy with the report of 70 operations.<sup>4</sup> The mortality was low, 2 deaths, functional results were excellent, and the authors were enthusiastic about the operation.

There are reasons to believe that retropubic prostatectomy will have a very thorough trial in this country. I do not agree that Millin's criticisms of present methods of relieving prostatic obstruction are entirely justified, but I admit that there is some truth in his comments on these procedures. Although the perfect method of removing the prostate may not have been devised, I am not prepared to hand the laurel to retropubic prostatectomy until the long-term results are clear. The urologist should be able to perform all the well recognized operations for the relief of prostatic obstruction.

### *Carcinoma of the Bladder*

The classification of epithelial tumors of the bladder has always been confusing, and no one classification of these neoplasms has been generally accepted. The Tumor Registry of the American Urological Association, after a study of over 1200 sections of these tumors in 1936, decided that it was not practical to segregate bladder neoplasms into definite groups corresponding to their cell types. Jewett and Blackman,<sup>5</sup> after a histologic study of 97 cases of bladder tumor in which autopsy was performed, concluded that accurate classification of large infiltrating carcinomas of the bladder on the basis of cellular differentiation alone was impossible. Many classifications of these tumors in the past have been confusing because they were too complicated.

The present tendency is toward a simpler classification. In 1939 Ash<sup>6</sup> stated that morphologically the tumors fall into two groups, papillary and sessile. For the past seven years epithelial tumors of the bladder at the Massachusetts General Hospital have been classified as papillary and nonpapillary. Tumors in each of these groups are graded I, II or III according to their microscopical appearance.<sup>7</sup> Either the papillary tumors or the nonpapillary (sessile) tumors may infiltrate. This simple classification is essentially the same as that used by the Bladder Tumor Registry, as outlined by Dart<sup>8</sup> and Ash.<sup>9</sup> It has the advantage of correlating the gross or cystoscopic appearance of these tumors with their histologic characteristics. Most bladder

## MENINGOCOCCAL PNEUMONIA\*

## Report of Two Cases with Meningococcal Effusion in One

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WITHIN a period of a month in 1942, 2 cases of pneumonia in which the meningococcus was implicated, without meningeal involvement, were observed. It has been known for some time that extrameningeal meningococcal infections are not uncommon,<sup>1</sup> but the attention directed to the respiratory phase of such infections is very scant. In view of the uniqueness of one of the cases observed and because of the lack of recent literature on the subject, it seemed worth while to report the cases and briefly to review the literature. The fact that most of the cases previously reported involved military personnel in World War I also affords an opportunity to review similar experience in World War II.

## CASE REPORTS

P. C. (B.C.H. 1088509) a 56-year-old man entered the hospital on November 24, 1942 because of chills and fever, cough and vague chest pain of 4 days duration. Physical examination revealed moist rales in the right axilla and a roentgenogram on the day of admission was reported as showing pneumonia of the right middle lobe. A blood culture taken before exhibition of sulfadiazine revealed a growth of Type 1 meningococcus. Neufeld typing of the sputum was reported as negative.

On sulfadiazine therapy from November 24 to 30 the patient made an uneventful recovery. A repeat x-ray film on December 3 was reported as being within normal limits. The white-cell count dropped from 14,100 on entry to 9,150. Blood cultures on November 29 and December 7 revealed no growth and the patient was discharged on December 10.

In this case of pneumonia routine blood cultures showed a growth of Type 1 meningococcus. Since Neufeld typing of the sputum was negative for both the pneumococcus and the meningococcus the evidence that the pneumonia was meningococcal in origin is indirect but warrants attention. The response to sulfadiazine was characteristic of that expected in either pneumococcal or meningococcal infections and did not resemble the response of pneumonias of virus etiology.

L. L. (B.C.H. Case 1090910†) a 33-year-old haker's helper was admitted to the hospital on December 21, 1942 with complaints of pain in the left side of the chest of 3 days duration, hemoptysis of 3 days duration and rash on the legs of 1 day's duration. For the past 2 weeks the patient had a "heavy" cough and had expectorated slight amounts of mucoid sputum which was occasionally blood streaked. Although not feeling too well, he had been able to work "heavily" every day. However 3 days prior to admission he noticed a sharp pain in the left maxillary region accompanied on deep breathing and coughing. Expectoration of

thick rusty sputum was noted on the same day. The symptoms became increasingly severe. On the day before admission a chill and fever were noted and, for the first time a red rash was seen on both lower extremities. The skin lesions were not painful, itchy or raised above the skin surface. The patient denied any previous similar manifestations.

The patient was unmarried and had been on relief for many years. He was a known chronic alcoholic of many years' standing. At the age of 20 he had had a penile sore and had been told that he had had blood many years before the present episode.

In January 1938 he had been seen in the Outpatient Department for shortness of breath. A positive blood Hinton test was noted. Physical examination showed an aortic diastolic murmur and the diagnoses of late latent syphilis, syphilitic heart disease with aortic regurgitation and generalized arteriosclerosis were entered in the record. A 7 foot roentgenogram of the chest revealed widening of the ascending and descending aorta raising the question of aortic aneurysm. After a few intramuscular injections of bismuth in oil had been given the patient absented himself from the clinic.

Physical examination disclosed a markedly dyspneic poorly nourished man who grunted with every respiration. The face was flushed, and dilatation of the alae nasi was noted. Over the thighs, feet and legs there was a petechial rash the lesions being pin point to 3 mm. in diameter, some were discrete and others confluent and did not blanch on pressure. The teeth were in very poor condition but the gums were firm and no bleeding was noted. The neck was supple, and Kernig and Brudzinski signs were absent. Examination of the chest revealed limitation of respiratory excursions of the left hemithorax. Decreased tactile fremitus, marked diminution of breath and voice sounds and dullness on percussion were noted over the lower half of the left portion of the chest, extending up to the level of the third rib anteriorly and the fifth thoracic vertebra posteriorly. The trachea was deviated to the right. The apical impulse was not made out on palpation; there was sinus rhythm with a rate of 100 per minute, and no aortic diastolic murmur was heard best in the third left interspace. Neurologic examination was not remarkable. The patient was somewhat incoherent and confused but cooperative and euphoric.

The temperature was 101.8 F., the pulse 118 and the respirations 34. The blood pressure was 130/100.

Examination of the blood demonstrated 110 gm. of hemoglobin and a white-cell count of 8950 with 84 per cent neutrophils and 17 per cent lymphocytes. The hematocrit was 36 per cent and the corrected erythrocyte sedimentation rate 35 mm. in 1 hour.

The sputum was thick, rusty and tenacious. Gram's stain revealed the sputum to be loaded with gram negative diplococci, the polymorphonuclear cells burst with these gram negative diplococci which had the morphology of meningococci. A number of gram positive diplococci outside the polymorphonuclear cells were also noted. Neufeld typing and culture revealed predominantly Type 1 meningococci with some Type 15 pneumococci.

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Blood cultures on admission before institution of chemotherapy and on the 3rd and 13th hospital days were negative for the meningococcus. Urinalyses were not remarkable, and there was a positive blood Hinton test but negative spinal-fluid Hinton and Wassermann tests. The spinal-fluid examinations, including culture, were not remarkable.

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The bacterial seed studies in this case were made in the laboratory of Dr. Maxwell Finland, at the Thorndike Memorial Laboratory, Boston City Hospital.

The patient was given 5 gm of sodium sulfadiazine intravenously on admission and in the usual oral dosage, adequate blood levels were obtained. Rumpke-Leede's test on the day of admission and on several subsequent days was negative for petechiae. The rash on the legs began to fade on the 2nd hospital day and had completely disappeared 5 days later. The sputum and chest fluid on the 3rd hospital day, as well as on subsequent examinations, were negative on culture for the meningococcus. It was apparent that a unique extrameningeal meningococcal infection, causing pneumonia, pleurisy with effusion and skin rash, was involved.

For the first 5 hospital days, the patient improved remarkably, and the signs in the left side of the chest appeared to be clearing. The bacteriologic studies and clinical course were convincing evidence that sulfadiazine was controlling the infectious process. At no time were signs of meningeal involvement present.

On the evening of the 5th day the patient became suddenly cyanotic and dyspneic, frothy pink sputum being expectorated. This typical attack of pulmonary edema was controlled by the use of intranasal oxygen and intravenous aminophylline. The patient was digitalized with moderate speed. A vital-capacity determination on the 8th hospital day was 30 per cent of normal.

In the remaining 7 hospital days the problem was essentially one of treating acute left ventricular failure. There were repeated bouts of pulmonary edema, dyspnea and cyanosis. The patient during this period was hallucinated and at times maniacal, requiring marked restraint and sedation. In spite of all the usual methods of therapy, he died on the 13th hospital day during one of these episodes.

Autopsy was performed 15 days post mortem (the interval after death precluded definitive bacteriologic study). Cardiac failure was thought to be the cause of death, as evidenced by pulmonary congestion and edema, chronic passive congestion of the liver and congestion of the spleen and kidneys. The left lung showed an organized confluent bronchopneumonia. The heart revealed severe coronary-artery atherosclerosis, with calcification and dilatation of the ascending aorta. Histologic study did not confirm the clinical impression of syphilitic aortitis or valvulitis.

In this case meningococcal pneumonia and pleural effusion were present without meningeal involvement. The patient did well on chemotherapy so far as the infective process was concerned but, as autopsy showed, died of heart disease. The post-mortem finding of a confluent bronchopneumonia was also reported in the autopsy material of Fletcher.<sup>2</sup>

### DISCUSSION

Osler<sup>3</sup> and others have pointed out that pneumonia is frequently described in certain outbreaks of epidemic meningitis, but the etiology of these pneumonias is not clear. The first recorded cases of primary meningococcal pneumonia were those of Jacobitz,<sup>4</sup> who reported 12 patients among a company of soldiers infected by the meningococcus. He divided the cases into five groups: typical meningococcal meningitis (2 cases), meningococcal pneumonia in association with meningitis (3 cases), pneumonia without meningitis (in a case in which sputum and nasopharyngeal examinations revealed meningococci and the symptoms included pyrexia ending by crisis, rusty sputum and signs of consolidation), bronchial catarrh without meningitis, the sputum containing meningococci (4 cases), and lung infections in which the meningococcus was found mixed with other bacteria (2 cases).

Sophian<sup>5</sup> mentioned a case in the 1912 Kansas City meningitis epidemic of a woman who had pneumonia

and was treated for four days, during which many meningococci were present in the sputum. She then developed meningococcal meningitis.

Osler<sup>3</sup> reported that 8 cases of pneumonia occurred in a Boston epidemic of cerebrospinal fever, but he did not give the bacteriologic findings.

During the influenza epidemic of 1918-1919, impetus to the study of meningococcal pneumonia occurred because of the complicating bronchopneumonias. This was especially true among American troops in England and France. Fletcher<sup>2</sup> reported the bacteriologic findings in post-mortem examinations of 36 patients who had died from bronchopneumonia following influenza contracted on a transport ship from the United States. In 11 cases the meningococcus was the predominant organism, but in each case *Haemophilus influenzae* was also present. Kinnicutt and Binger<sup>6</sup> found at autopsies in 47 cases of postinfluenzal bronchopneumonia at a base hospital in France that lung cultures were positive for the meningococcus in 19. It is also interesting to note that in 50 cases of bronchopneumonia in which blood cultures were taken, 10 per cent revealed growth of meningococci and terminated fatally. Meader, Means and Hopkins,<sup>7</sup> reporting on American troops in England, observed 5 cases of meningococcal pneumonia among 188 cases in which lung cultures were done at autopsy.

Probably the most complete work on this subject was done by Holm and Davison<sup>8</sup> and Davison, Holm and Emmons.<sup>9</sup> At a camp in France they studied 403 cases of pneumonia, many of which—but not all—were postinfluenzal pneumonias. Of these cases, 85 showed meningococci in the sputum. Of the 78 patients who died of pneumonia and were studied by culture at autopsy, 23 revealed meningococci in the lungs. Of these, 7 gave pure and 16 gave mixed cultures. From the studies, it was concluded that the meningococci may produce either bronchopneumonia or lobar pneumonia and that, because of the similarity of the organisms found in these cases to those found in the spinal fluids of patients with meningococcal meningitis, cases of meningococcal pneumonia may arise from cases of meningococcal meningitis and vice versa.

Reimann<sup>10</sup> states that the pleura is seldom involved in cases of meningococcal pneumonia. The cases reported in the literature substantiate this statement. The only case, other than the one recorded above, in the available literature was reported by Herrick<sup>1</sup> in a soldier who had bronchitis and later developed pleurisy with effusion and empyema. Culture of the aspirated chest fluid revealed a growth of meningococci.

The great majority of the cases of meningococcal pulmonary infection in World War I were associated with the complicating pneumonias of the severe influenza epidemic then prevalent. During World War II the severe pandemic type of influenza did not occur, although scattered, milder epidemics

were occasionally reported. It is therefore quite interesting that the only pertinent paper found in a review of the available literature since the onset of World War II was that of Roberg,<sup>11</sup> who reported a case in which a severe meningococcal pneumonia developed five weeks after recovery from pneumonia, probably of viral etiology. In this case the sputum smear showed gram-negative intracellular diplococci and the sputum culture revealed 75 per cent meningococci and 25 per cent hemolytic streptococci (Group A). A blood culture taken prior to sulfadiazine therapy was negative. The patient had a morbilliform rash. Roberg indicates that if the sputums in cases of pneumonia were routinely cultured under conditions favorable to the growth of the meningococcus, recognition of meningococcal respiratory infection would be made more frequently than is indicated by the paucity of reference to this entity in the literature.

#### SUMMARY

A case of meningococcal pneumonia with meningococcal pleural effusion is presented, and the literature reviewed.

### CLINICAL NOTE

#### AN UNUSUAL COMPLICATION OF INTESTINAL INTUBATION\*

MAJOR ADDISON G. BRENIKER, JR., M.C., A.U.S.

THE value of intestinal intubation for decompression by suction is so widely recognized that it is used extensively as a diagnostic and therapeutic adjunct. The Miller-Abbott and similar tubes, however, require the same working precision as any other instrument, and their proper function needs the attending physician's constant care to prevent complications.<sup>1,2</sup>

Most of the complications are familiar to all who have employed intestinal intubation. None are so serious as to condemn wide use of the procedure, but all are to be avoided if possible. The following is a list of minor hazards, some of which may seriously interfere with satisfactory decompression: difficulty or inability to introduce tubes into the duodenum<sup>1-3</sup>; minor epistaxis, transient pharyngitis or eustachian salpingitis, leaking or transposed adapters, leaking or ruptured balloons, leaking tubing, coiling in the stomach<sup>4,5</sup>; blocking of the suction lumen with intestinal contents, and accumulation of secretions proximally.

Other reported complications, such as acute otitis media, laryngeal edema or necrosis,<sup>6</sup> gastrointestinal

In epidemics of meningococcal infection with or without meningeal involvement, careful bacteriologic studies will probably uncover more cases of meningococcal pulmonary involvement than are reported at present.

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hemorrhage,<sup>7</sup> perforations, obstruction or intussusception from overdistended balloons<sup>8</sup> and knotting of the tubing distal to the gastric cardia,<sup>9,10</sup> may seriously endanger a patient's life, even when promptly treated and may necessitate additional surgery at a most inopportune time.

The following recently encountered case is illustrative of a complication that is of interest because of its unusual character and the fact that a few simple precautions may prevent its occurrence.

A 17-year-old soldier was admitted to hospital on February 19, 1947, with the typical history and physical findings of acute appendicitis of 24 hours duration. At operation a gangrenous appendix, which was perforated, no removal was found. In spite of parenteral antibiotics and Ochsner treatment a generalized peritonitis developed. On the 5th day a pelvic abscess was noted on rectal examination. Although greatly doze palpation apparently caused intraperitoneal rupture of the abscess, which was successfully drained through the rectum 4 days later. A subhepatic abscess, which subsequently localized, was drained on the 12th day after appendectomy.

On an attempt to begin oral feeding on the 13th day the patient developed abdominal cramps, nausea, vomiting, distention and obstipation. Roentgenograms of the abdomen showed dilated small intestine patterns with dependent fluid levels. A Miller-Abbott tube with 2 cc. of mercury in the balloon<sup>1</sup> was passed into the stomach and attached to constant suction. After repeated unsuccessful attempts the tube finally passed through the pylorus spontaneously on the 5th day. Fortunately during this period decompression progressed satisfactorily with intragastric suction; the patient remained afebrile, was relieved of pain and maintained a slow pulse and the abdomen remained nontender.

In the next 48 hours the tube progressed rapidly to a point in the left lower quadrant from which it moved slowly if at all. Five days after passage beyond the pylorus the 3 foot mark had not reached the external nares. Under fluoroscopic observation thin barium sulfate suspension was introduced to determine the site and extent of the obstruction.<sup>1</sup> The barium was seen to pass very slowly through a 5-cm. seg-

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ment of jejunum whose lumen was persistently constricted to 3 or 4 mm and thence into normal bowel. However, the most remarkable finding was that just proximal to this obstruction the tube was tightly coiled through two full turns into which the distal end had passed to make a simple (straight) knot. An attempt was made to withdraw enough tube to uncoil its distal end, and traction to the point of pain was made. This resulted in straightening of the normal curves at the gastric cardia, duodenum and ligament of Treitz but failed to move the coiled, distal end.

Since the point of obstruction had been demonstrated, and the patient had been decompressed, adequately hydrated and was in good electrolyte balance, immediate operation was performed. The abdomen was opened through a left paramedian incision, and an obstructing omental adhesive band was



FIGURE 1 Film Showing Conclusively the Presence of Two Complete Coils about the Mercury-Weighted Balloon

readily located about 4 feet distal to the ligament of Treitz. The tube was found to be tightly coiled and knotted proximal to this point, but it was possible to untie the knot and withdraw the tube without opening the bowel. The patient subsequently made an uneventful recovery.

### DISCUSSION

Looping and coiling of intestinal tubes in the stomach is very commonplace, and the practice of feeding excess lengths of tubing into the stomach without frequent radiologic check-up is universally condemned.<sup>5</sup> On the other hand coiling or knotting of tubing in the lumen of the small intestine is most unusual, particularly in the absence of redundant loops behind the advancing tip. To produce such a

complication there apparently must be dilated bowel proximal to a nearly complete obstruction, hyperactive peristalsis and a tube that is quite flexible or has previously been deformed by storage in a tight coil.

The tube used in the case reported above was not new, was moderately flexible and was found to have been stored in a tight coil for a considerable length of time. The use of a mercury-weighted balloon probably carried the tip to the point of obstruction more rapidly<sup>5</sup> than the rate of proximal decompression and may have played an indirect role in the coiling process. The weight of mercury in the balloon apparently caused the tip of the tube to prolapse through the coils (Fig 1) and produce a straight knot, which was tightened when extraction was attempted. Therefore, it seems reasonable to call attention to this possibility of coiling at an obstructed point with the use of the Harris single-lumen, mercury-weighted rubber tube<sup>5</sup> or the even more flexible, nonopaque, single-lumen "Koroseal" tubing described by Millet.<sup>7</sup>

It seems likely that this complication may be prevented by the following precautions: storage of all types of intestinal tubing in broad loops or, preferably, in linear fashion by vertical suspension, avoidance of introducing redundant loops of tubing without repeated radiologic check on the progress of the tip, and demonstration of the site and relief of obstruction as soon as practicable after the forward progress of the tip definitely stops.

### SUMMARY

The more frequent complications of intestinal intubation are considered.

A case is presented in which a mercury-weighted Miller-Abbott tube spontaneously coiled and tied itself into a simple knot in the jejunum proximal to an obstructing omental adhesion. This complication was apparently produced by the use of a flexible tube, previously deformed by long storage in a tight coil.

Ideally, intestinal tubes should maintain slight inflexibility and should be stored without coiling deformity, and their progress through the intestine should be followed carefully by x-ray observations.

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## THE SIGNIFICANCE OF "TICS" AS POSSIBLE MANIFESTATIONS OF EPILEPSY\*

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IN DESCRIBING the numerous manifestations of epilepsy, recent textbooks of neurology<sup>1-3</sup> discuss a great variety of motor phenomena but do not include the so-called "tics" as possible manifestations of epileptic disorder. However, in the older literature<sup>4-6</sup> the coexistence of epilepsy and tic was noted frequently enough to raise the question of an etiologic relation between the two, although conclusions regarding such a relation were generally believed to be premature. With the introduction of electroencephalography a new technic has become available, promoting a broader knowledge of epilepsy and permitting a re-evaluation of questions concerning epileptic manifestations. During the past two years I have observed 3 cases of tic in which, with the aid of electroencephalographic study, a diagnosis of epilepsy was made and in which, on the basis of all the evidence available, it appeared that the tics were true manifestations of epilepsy and not unrelated findings.

## CASE REPORTS

**CASE 1.** A 12-year-old boy was first seen on May 18, 1946, having been referred for treatment of a facial tic, which had been present for approximately 1 year and was considered a psychoneurotic manifestation.

The past history revealed that from the age of 6 years the patient had displayed several other types of motor phenomena (interpreted as "nervous habits") as follows: brief opening and closing of both fists, brief jerk of the head to one side with immediate return to the midline, sudden opening and closing of the mouth and sudden wrinkling of the forehead. Each type of motor pattern occurred several times daily for a few months and was then replaced by one of the others.

The patient was considered intelligent and was doing well in the 7th grade of school. There was no history of serious illnesses. The family history revealed that the patient's father had epilepsy; his attacks were of the grand mal type and had occurred about once every 2 years since the age of 15.

On neurologic examination the only positive finding was the occurrence of brief twitching of the orbicularis oculi muscles primarily on the right side occurring every few seconds. The patient was co-operative but seemed slightly embarrassed during the examination.

An electroencephalogram<sup>7</sup> showed a great deal of slow-wave activity with marked shifting asymmetry. There were definite discharges of typical 3 per-second spike and wave activity at rest and these were greatly exaggerated during overbreathing.

On treatment with 90 mg. of Mebaral twice daily the tic completely disappeared and there were no unpleasant side effects of this medication. When the therapy was changed to tridione the twitching occurred more frequently than prior to the first visit. Therefore the patient was maintained on 90 mg. of Mebaral twice daily with control of twitching until the last examination 1 year later. Shortly before the last examination experimental withdrawal of Mebaral was followed by a return of the tic within 48 hours.

However when the drug was readministered, there was again complete control.

**CASE 2.** A 9-year-old boy was first seen on August 1, 1946, because of a "facial tic" of 1 year's duration. Prior to his visit the patient had consulted an oculist because it was thought that he required glasses; the eyes were found to be normal, and he was then referred for psychiatric study.

The past history revealed that at the age of 1 year the patient had had a generalized convulsion and had been hospitalized for 4 days. A diagnosis of acute tonsillitis was made at that time. There were no other generalized convulsions up to the time of his first visit.

The patient had recently completed the 3rd grade of school with high marks. Although his behavior was described as satisfactory it had been observed that he was at times, slightly irritable.

Neurologic examination was negative except for the occurrence of brief twitching of the orbicularis oculi muscles every few seconds. The patient was co-operative and friendly; he was not shy or fearful.

An electroencephalogram showed a great deal of high-voltage slow wave activity in the frequency range of 4 to 7 per second occurring in groups and also as scattered waves. During overbreathing there was a very large build up with the occurrence of episodic high voltage 3 per-second waves but no spikes. Although the tracing was suggestive of petit mal activity there were no typical petit mal waves.

Treatment was started with 30 mg. of phenobarbital three times daily. One week later the patient showed marked improvement, no twitching of the orbicularis oculi muscles was observed. However further study was not possible because the mother was unwilling to have her son take regular medication.

**CASE 3.** A 14-year-old boy was first seen at the Southard Clinic on March 13, 1946, because of a history of repeated twitching of the head of 1 year's duration. Several times daily the patient's head jerked slightly to the right and then promptly returned to the midline.

The patient had been a behavior problem since the age of 5. He was a oaf hater, was at times stubborn, rude or disagreeable and frequently disobeyed his parents, 2 weeks before entry he had been arrested with a group of boys for breaking into a store. However he was doing well in the 9th grade of school.

Neurologic examination was negative except for the appearance of an occasional slight twitch of the head to the right with a rapid return to the midline. During the interview the patient was somewhat evasive and seemed resentful at having been brought to a psychiatrist for examination.

The electroencephalogram showed paroxysmal high voltage discharges occurring at rest. On overbreathing there was a large build up, with the appearance of numerous high voltage 3 per-second waves some associated with small spikes. The tracing was consistent with epileptic disorder of the petit mal variety.

The patient was given 90 mg. of Dilantin Sodium three times daily, and after a few days the so-called "tic" disappeared. Three months later the medication was discontinued and during the subsequent 4 months of follow up observation there was no recurrence of twitching.

## DISCUSSION

In all 3 cases presented above the electroencephalograms showed epileptic dysrhythmias. In 1 case the electroencephalogram revealed classic bursts of 3-per-second spike and wave activity, diagnostic for the petit-mal epilepsies. In another case bursts of 3-per-second waves with small spikes occurred,

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Electroencephalograms were recorded at the Boston Psychopathic Hospital and were interpreted by Dr. Milton Greenblatt.



although not classic, this tracing was also considered characteristic for petit-mal epilepsy. In the third case, although the dysrhythmia was of the high-voltage, slow-wave, 3-per-second variety, the absence of spikes made the tracing only suggestive of petit-mal dysrhythmia. However, when all three electroencephalograms were viewed together one obtained the impression that they represented similar dysfunctions. In each case a diagnosis of idiopathic epilepsy was made.

It is my opinion that these 3 cases represent atypical forms of myoclonic epilepsy. In favor of this opinion is the electroencephalographic finding of 3-per-second spike and wave dysrhythmia, which, according to Lennox,<sup>7</sup> is characteristic of myoclonic epilepsy as well as of petit-mal and akinetic epilepsy. Tics have a resemblance to myoclonic jerks, and although in the usual forms of myoclonic epilepsy brief contractions of muscles in the upper extremities occur, at times similar contractions of other muscles are seen.<sup>7</sup>

Tics are usually considered to be manifestations of neurotic disorders.<sup>8</sup> One should therefore consider the possibility that the tics in these cases were of psychogenic etiology and that their occurrence in patients with epileptic dysrhythmia was merely a coincidence. This possibility cannot be entirely excluded with the limited evidence available. However, it appears to be more likely that the tics described were true manifestations of epilepsy, not only in view of their resemblance to myoclonic phenomena and the rather characteristic electroencephalographic findings but also because of the pronounced response to relatively small doses of anticonvulsant medication without the appearance of drowsiness or other side effects.

Wechsler<sup>2</sup> states that, although most observers have assumed tics to be psychogenic, the fact that they occur at times on the basis of brain damage—for example, as a sequel to epidemic encephalitis—should lead one to question routine psychogenic explanations of their origin. He states that the precipitation or aggravation of tics by emotional factors does not argue in favor of a completely psychogenic explanation because many definitely “organic” movements are similarly affected by emotional fluctuations.

In view of these considerations it appears reasonable that more cases with tics should be studied from the electroencephalographic point of view to clarify the question whether there is an underlying epileptic dysrhythmia. Although it is expected that few such patients will be found to have epilepsy, this diagnosis should be kept in mind when the problem of tic presents itself.

#### SUMMARY

Three cases are reported in which tics appeared to be manifestations of epilepsy. It is suggested that more cases with tics be studied by electroencephalography to determine the incidence of epileptic dysrhythmia in this group of disorders.

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## INFECTIOUS MONONUCLEOSIS WITH INTENSE JAUNDICE OF LONG DURATION\*

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**J**AUNDICE in infectious mononucleosis was first described in 1923 by Downey and McKimlin.<sup>1</sup> Since that time, scattered reports of its occurrence have appeared.<sup>2-21</sup> Martin,<sup>8</sup> in 1941 described 13 previously reported cases. In 1944 Boger<sup>17</sup> found 27 cases, and Spring,<sup>14</sup> in the same year, estimated that 35 cases had been recorded. Wechsler<sup>21</sup> discovered an additional 25 cases and reported 34 cases of his own from an epidemic of infectious mononucleosis. Thus, at least 100 cases have been described. This figure is in no sense an adequate reflection of the frequency of clinical jaundice in infectious mononucleosis, since undoubtedly many cases remain unreported. In different series, the incidence of jaundice has ranged from 0 to 13 per cent.<sup>1, 11, 19-21</sup>

The following case is presented because of the extreme severity of the hepatic involvement.

## CASE REPORT

**F**G., a 30-year-old man entered the hospital complaining of jaundice of 3 weeks duration. Five weeks before admission he had noted the onset of anorexia. One week later the urine became dark, and he began to experience easy fatigability and weakness. Three weeks before admission the skin became yellow and the stools light. He had no abdominal pain throughout this period but lost 30 pounds in weight. During the week before admission pruritus became pronounced. He had had a low-grade temperature for a few weeks and bad sensations of chilliness and generalized mild aches. The remainder of the history was inconsequential.

Physical examination disclosed a large-framed muscular markedly jaundiced man in no acute distress. A few petechiae and ecchymoses were present on the upper anterior portion of the chest wall. In the axillary and inguinal regions bilaterally small lymph nodes 1-2 cm in diameter were palpable. No cervical or epitrochlear nodes were felt. Examination of the chest was negative. The liver edge was palpated 2 cm below the costal margin and was nontender. The splenic edge was 2 cm below the costal margin and firm in consistency. The remainder of the examination was negative.

The temperature was 101°F. Examination of the blood revealed a hemoglobin of 12.5 gm per 100 cc. and a white-cell count of 4500 with 21 per cent neutrophils, 54 per cent lymphocytes, 15 per cent monocytes, 5 per cent eosinophils, 1 per cent basophils, and 4 per cent stab cells. Many of the lymphocytes had foamy vacuolated cytoplasm, kidney bean and clover shaped nuclei. Increased azurophilic granulation and "folding-over" of the cytoplasm. The heterophil-antibody test was negative at that time although the patient had been ill for 5 weeks.

The icteric index was 210, and the van den Bergh reaction immediate direct and indirect, with a bilirubin of 20.0 mg per 100 cc. The alkaline phosphatase was 4 units, the cholesterol 149 mg per 100 cc., with only a trace of esters, and the cephalin-flocculation test was negative. The total protein was 5.4 gm per 100 cc., with an albumin of 3.6 gm and a globulin of 1.8 gm. A stool was negative for bile. The urine was positive for bile but negative for urobilinogen. The prothrombin was 80 per cent of normal and the bleeding time was 2 minutes. On the intravenous hippuric acid test 0.42 gm was excreted in 1 hour (normal 0.8-1.3 gm).

X-ray study of the abdomen showed hepatomegaly and splenomegaly. There was no evidence of gall-bladder calculi.

Four days after admission the serum bilirubin rose to 27.5 mg per 100 cc. and a ++ cephalin flocculation test, which subsequently became +++ developed. Thereafter the icteric index began gradually to decrease. Bile appeared in the stool and urobilinogen in the urine. The icteric index dropped from 210 to 171 a week after admission to 61 within 2½ weeks of admission to 43 a week later and to 31 during the 5th and 7th during the 6th hospital week, and to 18 4 days before discharge. The hospital stay was 8 weeks.

During the first 3 weeks the temperature never rose above 102 F. and thereafter the level gradually returned to normal. Treatment consisted of a high-calorie, high protein, high carbohydrate low-fat diet, with added vitamins and lipotropic factors, and on this regimen appetite improved and the patient felt much better. No significant adenopathy developed. The liver and spleen remained palpable for about 6 weeks and were not felt thereafter. The total protein rose to 6.1 gm per 100 cc. and the albumin to 4.3 gm. The cholesterol reached 194 mg. and the cholesterol esters 82 mg per 100 cc.

A marked leukopenia was present throughout, the white cell count dropping to 2900 a week after admission and to 2000 on the following day. It remained below 5000 for about 7 weeks, reaching 5200 during the week before discharge. The peak of the lymphocyte percentage was 78 per cent, which was present 1 week after admission; the level thereafter gradually decreased until it reached 31 per cent the week before discharge.

Initially the heterophil-antibody test was negative. Two and a half weeks after admission a positive titer of 1:28 was reported, a week later the titer had risen to 1:112 and in the fifth week it rose to 1:896. At the time of discharge, the patient was faintly icteric, but otherwise well.

## DISCUSSION

Kulham and Steigman<sup>9</sup> have described an acute focal hepatitis with histiocytic reaction in infectious mononucleosis, and Ziegler,<sup>22</sup> has confirmed the presence of an acute inflammatory liver reaction. Cohn and Lidman<sup>23</sup> reported hepatic involvement, as judged by different liver-function tests, in 15 successive cases of infectious mononucleosis without jaundice.

Among 64 patients with infectious mononucleosis seen at the Long Island College Hospital during the past ten years, 6, or 9.4 per cent, showed jaundice clinically. The cephalin-flocculation test was performed on 25 of these patients, and was ++++ in 11 patients (44 per cent), +++ in 2 (8 per cent), ++ in 4 (16 per cent), + in 2 (eight per cent), doubtful in 2 (8 per cent) and negative in 4 (16 per cent). Thus, it was definitely positive in 52 per cent of cases and questionably positive in an additional 22 per cent. This suggests that a far greater number of patients with infectious mononucleosis have liver damage than the presence of clinical jaundice indicates, although it is known that other conditions than liver disease may cause a positive test.

The patient described above was visibly icteric for at least eleven weeks. The duration of the ill-

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ness, including the preicteric period, was thirteen weeks. He failed to develop a definitely positive Paul-Bunnell test until eight and a half weeks after the onset of the illness. The jaundice appeared initially to be obstructive in character, and yet there was definite evidence of an active hepatitis (the cephalin-flocculation test, the hippuric acid test and the ratio of cholesterol to cholesterol esters). The intensity of the hepatitis may have been linked to the late development of the usual serologic response to infectious mononucleosis. Thus, the possibility of a diminished immunologic defense mechanism must be considered. Although the presence of enlarged lymph nodes in the hilus of the liver could not be ruled out, there was sufficient evidence of acute hepatitis to establish this as the most probable cause of the jaundice.

Most cases of jaundice in infectious mononucleosis have been of short duration and slight intensity. Downey and McKinlay's<sup>1</sup> case in 1923 had a "faint and transient" jaundice. In the case reported by Fowler and Tidrick,<sup>6</sup> the jaundice disappeared in eight days. Martin,<sup>8</sup> reviewing the literature before 1941, stated that the jaundice seldom lasted longer than a week. Contratto<sup>13</sup> reported that the usual duration of icterus was not more than two weeks. In the 5 cases reported by Spring,<sup>14</sup> the jaundice lasted no longer than two and a half weeks. Kruger's<sup>19</sup> patient remained icteric for three weeks. Wechsler<sup>21</sup> found that three and a half weeks was the average duration of icterus in his 34 patients, 3 of whom remained icteric for over forty days. The longest duration of jaundice reported was 48 days.<sup>21</sup> None of the 6 cases studied at the Long Island College Hospital exceeded ten days in duration, with the exception of the case reported above.

Laboratory data reflecting the intensity of the jaundice were rarely presented. Wakefield and Mackay<sup>2</sup> found the bilirubin to be 5.6 mg per 100 cc, and in Fowler's<sup>6</sup> case it was 5.0 mg. The highest figures cited by Bernstein<sup>7</sup> in a comprehensive review of infectious mononucleosis in 1940, were an icteric index of 50 and bilirubin of 8 mg per 100 cc in the case described by Stuart, Burgess et al.<sup>3</sup> in 1934. The same figures were mentioned by Wintrobe<sup>25</sup> in 1942. Kilham and Steigman<sup>9</sup> reported 4 cases in 1942 in which the highest bilirubin was 7.5 mg per 100 cc. In the same year, Carter<sup>10</sup> observed a case in which the bilirubin was 22.0 mg per 100 cc, and Gold<sup>11</sup> described one with a bilirubin of 23.3 mg and an icteric index of 150 units. The highest figures in Spring's<sup>14</sup> cases were an icteric index of 74.3 and a bilirubin of 7.0 mg per 100 cc. In the cases reported by Monat,<sup>15</sup> Boger,<sup>17</sup> and Morris<sup>18</sup> the highest icteric index was 81. Wechsler<sup>21</sup> found 100 to be the highest icteric index in his cases, only 2 patients having levels over 80. The highest icteric index in

the group of cases at the Long Island College Hospital was 31 (except for the patient described above).

Thus, the jaundice of infectious mononucleosis has usually been mild, and its duration has rarely exceeded a month. In the case reported above the jaundice not only exceeded that of Gold's patient in intensity — the icteric index reaching 210 and the bilirubin 27.5 mg per 100 cc — but also lasted almost twice as many days as that in the longest case described. This case represents an extraordinary degree of hepatic involvement in infectious mononucleosis, no parallel for which has been found in the literature reviewed.

The profound leukopenia may have been related to the hepatic damage. Leukopenia is not uncommon during the first week of infectious mononucleosis, but usually the white-cell count rises before the temperature returns to normal.<sup>25</sup> Press<sup>20</sup> found leukopenia during the first week in 38 of 96 patients, during the second week, however, the white-cell count was normal or above in most cases. In the case presented above the white-cell count not only reached 2000 during the fifth week of jaundice but also remained below 5000 during the first seven weeks of hospitalization.

It should be pointed out that this case resembled a severe case of infectious hepatitis in all respects except the peripheral blood smear. The negative Paul-Bunnell tests during the first eight weeks of the illness might well have been accepted as evidence that this was, indeed, a case of infectious hepatitis, especially in view of the frequent occurrence of lymphocytosis and atypical lymphocytes in infectious hepatitis. The importance of repeated heterophil-antibody tests for long periods in suspected cases cannot be overemphasized. Probably many cases that failed to show the specific serologic response early in the disease have been labeled infectious hepatitis, when they actually represented one of the protean manifestations of infectious mononucleosis.

The therapy of infectious mononucleosis should be revised in the light of present knowledge of the frequency of liver involvement. Dietary therapy should be similar to that in infectious hepatitis, with a high-calorie, high-protein, high-carbohydrate diet. The early ambulation commonly allowed should be restricted in many cases. Certainly, bed rest should not be discontinued until laboratory evidence of hepatic involvement has disappeared. The experience of some patients, who have a long period of weakness and malaise after the illness is apparently at an end, might thus be avoided, and the possibility of recurrence or of permanent hepatic damage would be diminished.

#### SUMMARY

A case of infectious mononucleosis with intense jaundice of long duration is presented. The literature is briefly reviewed.

Of 64 cases of infectious mononucleosis at the Long Island College Hospital, 6, or 9.6 per cent, showed clinical jaundice. The cephalin-flocculation was strongly positive in 13 of 25 patients (52 per cent) on whom it was performed and questionably positive in 6 (22 per cent).

It is suggested that in doubtful cases in which jaundice is present, repeated heterophil-antibody tests be performed before infectious mononucleosis is ruled out.

Dietary therapy and bed rest are important in the management of infectious mononucleosis.

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## MEDICAL PROGRESS

### UROLOGY

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THE most frequent conditions treated by the urologist are those of the prostate and bladder. With the increased life expectancy that has taken place during the past twenty years, many more men reach the age when prostatic enlargement is likely to occur. The treatment of the obstructing prostate, therefore, deserves increasing consideration. Carcinoma of the bladder has always been a difficult problem, and its treatment in the past has not been too satisfactory. Some progress has been made in the understanding and treatment of both these diseases.

#### Retropublic Prostatectomy

Two years ago an entirely new procedure for the relief of prostatic obstruction was described by Millin,<sup>1</sup> of London. This operation is called retropublic prostatectomy and the author believes it to be original although a similar approach was used by van Stockum<sup>2</sup> in 1909.

The features of the operation as described by Millin are as follows: it is an extravesical procedure, it is applicable to all types of prostatic obstruction, it is relatively short and free of shock, the anatomic

approach to the prostate is a reasonable one, since no important structures are endangered, the mortality is low, the postoperative course is better (the postoperative stay in the hospital is seldom over two weeks), and all obstructing tissue is removed.

In a discussion of other recognized operations for the prostatic Millin made the following comparison:

**Suprapubic operations.** These operations require 6 to 10 per cent and involve a long stay in comfortable convalescence. There is considerable blood loss during and after operation. Postoperative infection is high. There is a high incidence of secondary hemorrhage.

**Perineal operations.** Technical difficulties require a long period of preparation for the danger of urinary incontinence, damage to the rectum and persistent fistulas is great. No cure is difficult because of wound contamination from the rectum.

**Transurethral operations.** It is difficult to learn to do these operations efficiently. A considerable blood is lost when large glands are moved. Persistent postoperative infection is likely. There is a high incidence of secondary

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ture The operation results in incomplete removal of the gland and recurrent obstruction

Believing that these operative procedures were far from satisfactory, Millin studied, on cadavers, a new approach to the prostate He was convinced that since the prostate is essentially an extravesical organ, it should be removed by an extravesical approach As a result of his studies the retropubic operation was devised

*Preoperative preparation* The usual studies of renal and cardiovascular function are made before operation Intravenous pyelograms are obtained The patient is not catheterized unless there is urinary infection that fails to respond to treatment or unless renal function is poor Urethral-catheter drainage is avoided if possible

*Anesthesia* Low spinal anesthesia or Pentothal Sodium and nitrous oxide and oxygen are used The patient is cystoscoped for the first time on the operating table

*Operative technic* The bladder is exposed by a midline suprapubic incision The prevesical space is opened and cleared of fat A specially devised self-retaining retractor separates the rectus muscles and presses the bladder upward The veins on the anterior and lateral aspects of the prostate are exposed and carefully studied, since their distribution varies considerably These veins are situated in the prevesical layer of the pelvic fascia A large central vein arises from the deep dorsal vein of the penis, other veins lie on each side These veins are tied with the aid of a boomerang needle The prostatic capsule is opened transversely, and bleeding points are grasped between toothed forceps The incision is then carried down to the adenoma The apex of the prostatic mass is freed from the capsule, and the dissection is continued up to the bladder neck Here the prostate is freed by sharp dissection Bleeding points are controlled by ligature or electrocoagulation After removal of the hypertrophied gland a No 18 catheter is passed through the urethra to the bladder The prostatic capsule is closed with interrupted sutures The abdominal wound is closed, a small drain being left in the prevesical space

In his first 20 cases Millin reported no mortality and few postoperative complications Since this first report Millin has performed over 400 retropubic prostatectomies, which he described at the July, 1947, meeting of the American Urological Association in Buffalo, New York The mortality was approximately 4 per cent Millin's enthusiasm for the procedure was unbounded In his book describing the operation, he states that the extravesical retropubic approach to the prostate enables one to deal with all pathologic conditions within that organ and its contained urethra<sup>3</sup>

Among the audience who listened to Millin's presentation, there were a few skeptics, consisting of some who had seen Millin operate and who had

performed retropubic prostatectomies themselves Their enthusiasm seemed to be less than Millin's, tempered no doubt by their own experiences The prevailing opinion, however, was one of considerable interest and an eagerness to go home and "try it out"

Since then little has appeared in our own literature concerning this new method of removing the prostate, although the few reports available have been favorable

The recent French literature includes a description of retropubic prostatectomy with the report of 70 operations<sup>4</sup> The mortality was low, 2 deaths, functional results were excellent, and the authors were enthusiastic about the operation

There are reasons to believe that retropubic prostatectomy will have a very thorough trial in this country I do not agree that Millin's criticisms of present methods of relieving prostatic obstruction are entirely justified, but I admit that there is some truth in his comments on these procedures Although the perfect method of removing the prostate may not have been devised, I am not prepared to hand the laurel to retropubic prostatectomy until the long-term results are clear The urologist should be able to perform all the well recognized operations for the relief of prostatic obstruction

### *Carcinoma of the Bladder*

The classification of epithelial tumors of the bladder has always been confusing, and no one classification of these neoplasms has been generally accepted The Tumor Registry of the American Urological Association, after a study of over 1200 sections of these tumors in 1936, decided that it was not practical to segregate bladder neoplasms into definite groups corresponding to their cell types Jewett and Blackman,<sup>5</sup> after a histologic study of 97 cases of bladder tumor in which autopsy was performed, concluded that accurate classification of large infiltrating carcinomas of the bladder on the basis of cellular differentiation alone was impossible Many classifications of these tumors in the past have been confusing because they were too complicated

The present tendency is toward a simpler classification In 1939 Ash<sup>6</sup> stated that morphologically the tumors fall into two groups, papillary and sessile For the past seven years epithelial tumors of the bladder at the Massachusetts General Hospital have been classified as papillary and nonpapillary Tumors in each of these groups are graded I, II or III according to their microscopical appearance<sup>7</sup> Either the papillary tumors or the nonpapillary (sessile) tumors may infiltrate This simple classification is essentially the same as that used by the Bladder Tumor Registry, as outlined by Dart<sup>8</sup> and Ash<sup>9</sup> It has the advantage of correlating the gross or cystoscopic appearance of these tumors with their histologic characteristics Most bladder tumors

can be fairly accurately grouped and graded in this classification by cystoscopic examination alone.

It will be noticed that the term papilloma is omitted from this classification. Although these tumors do not have the histologic characteristics of malignancy, they are considered papillary carcinoma (Grade I). This is because their subsequent behavior is unpredictable. Ash<sup>8</sup> also avoids the term papilloma, since he regards it as impossible to determine by histologic examination how such tumors would behave clinically. Further basis for this point of view has recently been obtained from the work of Hovenan and Deming,<sup>10</sup> who report the successful heterologous transplantation of papillary tumors of the bladder in man to the anterior chamber of the eye of the guinea pig. One of their cases was that of a recurring papilloma of the bladder that had no evidence of malignancy. This tumor grew, however, in its transplanted site and thus established its identity as a true cancer.

A study of 107 post-mortem cases of bladder cancer was made by Jewett and Strong<sup>11</sup> to determine the relation of depth of penetration of the bladder wall to the incidence of metastases, lymphatic invasion and perivesical infiltration. The tumors were put into three groups: tumor cells confined to the submucosa, tumor infiltration extended into but not through the muscularis, and tumor cells extended through the muscular coat.

The curability in the first group is 100 per cent, that in the second group 86.6 per cent, and that in the third group 26 per cent. In other words, the incidence of local extravascular extension and metastases increases with the degree of penetration of the bladder wall. The most frequent sites of metastases are the regional lymph nodes, liver, lungs and bones, particularly the vertebrae and bony pelvis.<sup>12</sup>

The treatment of bladder cancer is changing, with more tendency toward radical surgery (total cystectomy). Complete removal of the bladder necessitates considerable serious surgery. The ureters must be transplanted to the skin or the large bowel. Skin ureterostomy is the safer procedure, but has obvious disadvantages. Evidence is accumulating that ureterointestinal anastomosis may be compatible with comfort and relative security. This has been adequately proved for nonmalignant diseases of the bladder such as exstrophy, but less so for cancer. Improved surgical technique, adequate preparation of the large bowel and the antibiotics have made ureterointestinal anastomosis a safer procedure than heretofore, with a mortality rate of probably from 10 to 20 per cent.<sup>13</sup> Higgins<sup>14</sup> recently reported no mortality from this operation in his last 22 cases.

The various methods employed in the treatment of bladder tumors are transurethral removal with or without radium, suprapubic operation with local

destruction of the tumor or partial cystectomy, total cystectomy and external radiation. Priestley<sup>15</sup> discusses the application of these different procedures to vesical neoplasm and describes the indications for each. Small, noninfiltrating lesions of low malignancy are best suited to transurethral treatment. Segmental resection of the bladder is employed for tumors that are well removed from the ureteral orifices, situated high in the bladder on the dome or lateral walls and of reasonable size. This method is generally used for infiltrating growths. The indications for total cystectomy are extensive low-grade lesions that involve most of the bladder or are present in many areas and frequently recur, highly malignant infiltrating tumors not removable by other measures and any neoplasm that cannot be removed completely without seriously affecting vesical function. External radiation is employed only in cases that are not suitable for surgery.

It is impossible at present to know how effective total cystectomy, as performed today, is as a cure for cancer of the bladder. In the past this operation has been done without the aid of modern methods of technique, preoperative preparation and the recent measures for controlling infection. Many patients whose tumors were so extensive that there was no reasonable hope of cure were formerly operated upon. As a result, the mortality was high, and complications were severe. Although total cystectomy involves a program of serious surgery, this procedure is becoming more simplified and standardized. It will doubtless be applied to more suitable cases and will eventually have a reasonable mortality.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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#### CASE 34091

##### PRESENTATION OF CASE

A sixty-three-year-old Italian-born garage worker entered the hospital for the first time because of weakness of eight months' duration.

About eight months before admission he had a single episode of finding blood on his pillow and in his mouth on awakening. There were no previous or subsequent hemoptyses or hematemeses, but a productive cough developed shortly after this episode and progressed in severity up to admission. About 2 glassfuls of greenish sputum were produced daily. He had no pain but developed moderate exertional dyspnea, weakness and fatigability that necessitated giving up his job shortly after the onset of the present illness. Anorexia contributed to a 45-pound weight loss, and in the last month he developed night sweats and ankle edema.

The past history revealed an episode of epigastric pain twenty-three years before entry diagnosed as "stomach ulcer" and successfully relieved by an ulcer diet, which was followed for only six months. Active duodenal ulcer was allegedly demonstrated by x-ray examination one month before the onset of the present illness.

Physical examination revealed a pale man showing evidence of recent weight loss. There was slight clubbing of the fingers and toes. Lymphadenopathy was generalized with pea-sized to cherry-sized, movable, nontender rubbery nodes in the cervical, supraclavicular, inguinal, axillary and left epitrochlear regions. The right side of the chest was splinted, appeared smaller than the left and was flat to percussion below the level of the fifth rib posteriorly and in the axillary line. Tactile fremitus and spoken voice sounds were increased over the right apex and absent over the right middle and lower lobes. Examination of the heart was not remarkable except for its apparent shift to the right. The liver edge was smooth and nontender and extended 3 cm below the costal margin. There was a 3-cm reducible left direct inguinal hernia.

The temperature was 99°F, the pulse 76, and the respirations 28. The blood pressure was 115 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 3,700,000 and a white-cell count of 10,400 with 72 per cent neutrophils, 22 per cent lymphocytes and 6 per cent monocytes. The urine was normal. Guaiac tests on the stools were negative. The serum protein was 6.7 gm per 100 cc, with an albumin-globulin ratio of 0.76, the nonprotein nitrogen was 25 mg per 100 cc.

X-ray examination of the chest showed an area of increased density, with a fluid level in the apical division of the right lower lobe, the mediastinum was shifted to the right, and the left lung showed compensatory emphysema. There was some fluid in the right costophrenic sinus. Smears of sputum for acid-fast bacilli were negative. Cytologic smear of the sputum showed tumor cells, and a bronchoscopy revealed an irregular stenotic area in the right upper-lobe bronchus.

The right axillary lymph node was biopsied.

##### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES: On first reading this seems like a fairly straightforward problem involving the differential diagnosis of bronchial stenosis with pulmonary atelectasis and infection. So far as the duodenal ulcer goes, I do not see how that can influence the discussion except so far as it might raise the question of whether the original episode of bleeding was hematemesis rather than a hemoptysis. When blood appears in the mouth as described here, it seems much more likely to come from the lung, but I see no way of settling that problem one way or the other.

At this point I think it might be wise to see the x-ray films.

DR STANLEY M WYMAN: Examination of the chest is not complete because we do not have an overexposed film to enable us to study the bronchi. The right base is denser than the left. The heart is deflected toward the right with the mediastinum and the trachea. There is an area of hazy homogeneous density occupying the lower middle third of the right lung field, and the right leaf of the diaphragm is obscured, probably by fluid. A definite cavity containing gas or fluid is seen close to the heart in the anteroposterior film and lying as described in the dorsal division of the right lower lobe. The right lower lobe appears decreased in size and appears to be airless. There is some compensatory emphysema in the right upper and probably right middle lobe. However, the patient had emphysema for many years, as seen by the increase in the anteroposterior diameter of the chest. There is probably some fine fibrosis through the left lung, which is otherwise clear. A film of the gastrointestinal tract shows the old deformed duodenum, which is consistent with a history of ulcer.

DR KRANE: Do you find any evidence of enlarged mediastinal lymph nodes?

DR WYMAN: I cannot be sure of any. The prominence in the region of the left hilus seems to be vascular, and no definite mediastinal lymph nodes are seen.

DR KRANE: No particular problem seems to be involved in this case until we come to the last sentence, about which a certain air of finality implies that the answer is to be found in the lymph-node biopsy. If that is so, it becomes more of a problem than was at first apparent, and it excludes immediately the one most common lesion that produces this clinical picture—namely, carcinoma of the bronchus. So far as I am aware, it is most unusual for carcinoma of the bronchus to metastasize generally to the lymph nodes without a good deal more evidence of metastases elsewhere. As a matter of fact, unless this was an extremely bizarre form of carcinomatous metastasis, I do not recall having seen simultaneous metastases to the inguinal, axillary, cervical and epitrochlear nodes. If the biopsy does give the answer, it excludes the possibility of carcinoma of the bronchus.

We come therefore to discussion of the more common types of lesions that produce simultaneous involvement of the lymph nodes and pulmonary parenchyma. There are not very many but the first that comes to mind is tuberculosis. Tuberculosis does cause cavitation and can cause bronchial obstruction due to inflammatory stricture, but I think there is little else in this picture on which to base a diagnosis of tuberculosis. The x-ray pictures are certainly far from typical. The negative sputum examinations are very much against it, and at this man's age (sixty-three) generalized glandular tuberculosis of the lymph nodes would be unusual. It is much more commonly a disease of younger persons. Even if the lymph node were tuberculous, I do not see why one need assume that the pulmonary lesion was. The diagnosis of the pulmonary lesion would have to rest on the finding of tubercle bacilli, but apparently they were not demonstrated.

Sarcoidosis is another possibility, but so far as I know, it does not produce bronchial obstruction or pulmonary cavitation. This is certainly not my idea of the x-ray picture of sarcoidosis. Would you entertain the possibility of sarcoid from these films, Dr Wyman?

DR WYMAN: No.

DR KRANE: A much more arresting possibility is lymphoma. Pulmonary cavitation and hemoptysis may occur in lymphoma and may be caused in one of several ways. The lymphoma may infiltrate the pulmonary parenchyma, central necrosis, cavitation and hemoptysis eventually resulting, or a mass of glands may cause extrinsic pressure on the bronchus, causing collapse and infection distal to the obstruction. Another possibility, of course, is

an endobronchial lymphoma, which is exceedingly rare.

Against lymphoma is the fact that there was no evidence of enlarged lymph nodes in the mediastinum to cause pressure on the bronchus, and furthermore, as I have already stated, intrinsic bronchial lesions have been described but are exceedingly rare. Another objection to lymphoma, although I cannot be sure of how valid it is, is the statement that tumor cells were found by the Vincent Laboratory in the cytologic examination of the sputum. I am doubtful whether lymphoma—that is, individual cells of lymphoma—can be identified as tumor cells by the Vincent Laboratory. I asked Dr Benjamin Castleman whether it would be possible to identify individual cells in a lymphoma as tumor cells. He said that he thought it might be possible if the tumor was exceedingly undifferentiated, such as a stem-cell lymphoma. Be that as it may, until I have seen it demonstrated I shall remain doubtful. A finding of tumor cells by the Vincent Laboratory still means carcinoma. The only way of making a diagnosis of lymphoma in this case—so far as the pulmonary lesion goes—is its response to x-ray therapy. If, following x-ray therapy, this lesion should completely disappear—with a dosage of about 1200 r—one would have to assume that it was lymphoma. However, should the lesion not disappear, it still might be lymphoma, because although x-ray treatment may be expected to cause regression of lymphomatous tissue or nodes, it could not be expected to reduce the secondary effects of the process such as infection. For the reasons that I have stated I doubt very much that the patient had lymphoma—at least in the lung.

If we disregard the lymph node, and I am afraid that I have to, we are on more familiar ground. The usual causes of this sort of picture in a person of this age are benign pulmonary abscess, which seems unlikely in view of the history and x-ray findings, and benign adenoma of the bronchus, which is consistent with everything described. Against the latter, however, is the patient's age, it occurs usually in the younger age group. Also against it is the fact that tumor cells were found in the sputum. A positive finding of tumor cells has usually been very significant and means carcinoma. Because of that fact and since the rest of the picture is so consistent with the diagnosis, I shall disregard the lymph nodes for the time being, and guess that the patient had a bronchiogenic carcinoma.

A PHYSICIAN: What was the result of the serologic test?

DR TRACY B. MALLORY: I think we can safely assume that it was negative.

A PHYSICIAN: Is it possible for a malignant tumor of the liver with metastases to the lung to invade the bronchus and give this picture?

DR KRANE: I think it is unlikely. Metastatic lesions to the lungs do not usually involve the



bronchi, but rather the lung parenchyma. Is that true, Dr Mallory?

DR MALLORY Yes

#### CLINICAL DIAGNOSES

Malignant lymphoma, lymphocytic type  
Squamous-cell carcinoma of lung

#### DR KRANES'S DIAGNOSIS

Bronchiogenic carcinoma

#### ANATOMICAL DIAGNOSES

*Epidermoid carcinoma (Grade II), of bronchus*  
*Malignant lymphoma, giant follicular type, of lymph nodes*

#### PATHOLOGICAL DISCUSSION

DR MALLORY We had two biopsies from this patient, one from the bronchus and one from a lymph node. They showed two entirely different types of tumor, the one from the bronchus was a squamous-cell carcinoma (Grade II), and the lymph node showed a giant follicular lymphoma. This has posed a great problem regarding treatment. It was believed that x-ray treatment of the lungs was more likely to do harm than good. Hence the tentative plan is to treat the patient with nitrogen mustard, which might influence both neoplasms.

### CASE 34092

#### PRESENTATION OF CASE

A twenty-seven-year-old dentist was admitted to the hospital because of persistent vomiting of twenty-four hours' duration.

The patient was said to have been in good health until one year before admission. He had served in the Navy for three years following graduation from dental school. His entire service had been in the United States. For about one year he had been thought to have a peptic ulcer and had occasional episodes of nausea and vomiting during that time. Five days before admission these episodes became more severe, and he was unable to go to his office. Twenty-four hours prior to admission persistent vomiting started, he became restless and was unable to sleep. When seen the morning of admission the patient was disoriented and obviously critically ill. Immediate hospitalization was advised.

The past history was noncontributory. One sibling had had pulmonary tuberculosis. There was no other history of familial disease.

Physical examination disclosed a hyperactive and disoriented patient. The skin was dry and diffusely tanned. There was no increased pigment in the folds of the skin. The lips and the nailbeds were dusky purple. There were multiple areas of pigment on the tongue about the color of egg plant. No pigment was seen on the buccal mucosa. There was a marked tremor of the tongue and extremities.

Motor activity was so great that special attendants were required to restrain the patient.

The temperature was 104°F, the pulse 134 and regular, and the respirations 24. The blood pressure was 50 systolic, 30 diastolic.

Examination of the blood revealed a hemoglobin of 13.2 gm, a hematocrit of 39 per cent and a white-cell count of 10,700, with 52 per cent neutrophils, 5 per cent young neutrophils, 4 per cent late myelocytes, 23 per cent lymphocytes, 13 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The blood Hinton test was negative. Urinalysis revealed a specific gravity of 1.010, a ++ test for albumin, a rare hyaline cast, frequent coarse granular casts, a rare red cell and 1 white cell per high-power field. The nonprotein nitrogen of the blood serum was 100 mg and the sugar 67 mg per 100 cc, the sodium 135.7 milliequiv, the potassium 6.8 milliequiv and the carbon dioxide 17.4 milliequiv per liter.

A lumbar puncture done on the second hospital day revealed an initial pressure equivalent to 200 mm of water, with the patient poorly relaxed. A Pandy test was negative. The spinal-fluid protein was 30 mg per 100 cc and the gold-sol curve was 0001111100. The cell count gave 6 red cells and 3 lymphocytes per cubic millimeter. The Widal and Weil-Felix tests were negative. An x-ray film of the chest taken with a portable machine showed no abnormality. An electrocardiogram disclosed auricular tachycardia at a rate of 160 but no other abnormality.

In the first twenty-four hours the patient received 3000 cc of 5 per cent dextrose in physiologic saline solution, 500 cc of whole blood, 900 cc of physiologic saline solution and 3 ampules of sodium racemic lactate intravenously. In addition he received 150 cc of Upjohn's cortical extract intravenously, 10 mg of desoxycorticosterone intramuscularly and 40,000 units of penicillin every three hours. During the next twenty-four hours he received 4500 cc of 5 per cent dextrose in physiologic saline solution, 550 units of plasma, 3 ampules of sodium lactate, 60 cc of Upjohn's cortical extract and 10 mg of desoxycorticosterone. The penicillin was continued. On the third day he received 3000 cc of 5 per cent dextrose in physiologic saline solution, 2 ampules of sodium lactate, 500 cc of whole blood, 60 cc of Upjohn's cortical extract and 10 mg of desoxycorticosterone.

The temperature ranged from 103 to 105°F. The pulse was never recorded below 130. The blood pressure rose to 129 systolic, 45 diastolic, on the second day after the plasma. On the evening of the third day after being maintained above 100 all day it fell in the late evening to about 80 systolic, 44 diastolic. Clinically he changed little. He remained irrational and hyperactive. On the third day he developed a bronze blush over the arms and upper trunk with the appearance of small vesicles containing honey-colored fluid. Late on

the third day the pulse rose to 190, and the blood pressure became unobtainable. Examination of the blood on the third day showed the sugar to be 139 mg and the nonprotein nitrogen 46 mg per 100 cc., the sodium 152.0, the carbon dioxide 24.0 and the chloride 116.0 milliequiv per liter. The patient died early on the morning of the fourth day.

#### DIFFERENTIAL DIAGNOSIS

DR MARIAN ROPES Since no definite statement is made, I shall assume that the lung and neurologic examinations were essentially negative.

DR DANIEL ELLIS That is right.

DR ROPES At the outset I can think of no condition that satisfactorily explains all aspects of the picture. It is my impression that the disease was of at least one year's duration and was not merely an acute episode. There are various groups of symptoms to consider. There are five major ones: the gastrointestinal symptoms, the pigmentation, the evidence of renal failure, the suggestion of adrenal insufficiency and the central-nervous-system symptoms. We are told very little about the gastrointestinal symptoms. The patient had nausea and vomiting, however, and it was thought that he had a peptic ulcer.

There are various conditions that one must think of with the combination of gastrointestinal symptoms and pigmentation. Porphyrria is one that comes to mind. However, there is relatively little else in the picture to support that diagnosis. The type of pigmentation is perhaps consistent with it, and the gastrointestinal symptoms surely are consistent. The absence of paralysis and the presence of as much irritation from the point of view of the nervous system are not consistent, and there is nothing else to support the diagnosis. He surely did not have the type in which a colored porphyrin is present in the urine.

One thinks of hemochromatosis, but in the absence of diabetes and liver enlargement and in the presence of definite renal involvement and marked central-nervous-system symptoms, this can be discarded relatively easily. Also, with the pigmentation and chronic involvement I wondered about the possibility of some type of poisoning. The diffuse pigmentation described was surely not that of argyria, and argyria would not explain the rest of the picture. Methemoglobinemia is suggested by the color of the lips and the nailbeds. Again, that would not explain the rest of the picture. There is no further evidence of this, nor is there evidence of any other type of poisoning.

One condition suggested by the gastrointestinal symptoms and pigmentation that must be considered is Addison's disease, with which nausea and vomiting over the course of a year would certainly be possible. However, it would be very unusual not to have had other symptoms — at least weakness during the same period. The pigmentation is in general consistent, the tongue and the skin are charac-

but with such marked pigmentation as I gather he had I would expect some in the folds of the skin. The pigmentation might be a racial characteristic, although we are not told what his race was and this would not explain the pigmentation on the tongue. Certainly, the final crisis could be consistent with that of adrenal insufficiency. Again, the degree of urinary changes was greater than that usually found during an adrenal crisis. Though uremia may occur I would be surprised to find as large a number of casts present during the crisis. Similarly, the central-nervous system reaction is greater than that usually seen in a crisis. However, in the presence of uremia this is relatively easily ascribed to uremia and not to any underlying adrenal failure. The fever again is much higher than one would expect and surely suggests the presence of infection. That brings up the question of the cause of the adrenal failure if present in this patient. There was a history of tuberculosis in the family. Tuberculosis is not the most common cause of adrenal failure, hypoplasia of the adrenal glands being a more common cause of Addison's disease. Similarly, the infection suggested by the fever and the cellular reaction in the blood raise the question of adrenal insufficiency secondary to an acute infection. Some of the laboratory tests are consistent with Addison's disease. The hypoglycemia is typical. The potassium is elevated, but the normal or low sodium is unusual with this degree of potassium elevation. In fact it is also interesting that a patient with elevation of potassium had a normal electrocardiogram except for the tachycardia.

For the moment, therefore, to leave adrenal insufficiency and consider one of the other possible explanations of the entire picture, I would swing to renal failure. There is no question that this patient had renal failure at the time of admission — whether primary or secondary is more of a question. The nausea and vomiting could easily have been due to a slow onset of renal insufficiency. It was present for a somewhat longer period than one commonly sees, but it was inside the limits of what is seen. There is no way with this diagnosis to explain the pigmentation. In my opinion it cannot all be related to the renal failure unless he had porphyria for which I find no other evidence. The degree of fever is not that seen in renal failure. The potassium elevation could have been due to the severe renal failure or to the associated shock, with passage of potassium out through the cells, so that in itself does not need to make one insist on the presence of adrenal insufficiency.

When one considers the possible causes of renal disease in this patient one notices first the relatively minimal urinary changes, the albuminuria with frequent granular casts. There were only rare red and white cells. This raises the question of some of the diseases in which such urinary findings are found commonly, such as myeloma and amyloidosis. I find nothing in the record to

myeloma. Similarly, I find nothing to suggest an underlying cause of amyloidosis. That does not rule out the possibility of amyloid disease of the kidney, but without further support it need not be considered further. When one thinks of periarteritis nodosa or other vascular change as a cause of the nephritis, there is again very little evidence in the rest of the picture for such a diagnosis. So, in terms of renal failure one should think of more common causes at this age, and with no evidence of history of urinary infection the possibility of glomerulonephritis should be put as the most likely explanation of the renal disease. I think that even if adrenal disease was present this patient also had renal disease.

I think that one must consider the possibility of infection in this case. I doubt that any infection that can produce this picture could have been present for a year and explain the earlier symptoms. That could be contradicted if one said that tuberculosis in some form might have been present, but the symptoms throughout the year would be very unusual for tuberculosis in the gastrointestinal tract or abdomen. I can think of no other infection that could explain the symptoms during the year. The terminal event suggests infection, but whether an underlying disease was precipitated by a severe infection is the question. The final rash means very little to me. A bronze blush with vesicles containing honey-colored fluid is difficult to explain but perhaps is suggestive of infection or possibly a disease of unknown cause, such as erythema multiforme exudativum. The lesions described would fit that disease, but in the absence of mouth lesions, eye lesions or anything else consistent with the picture, erythema multiforme exudativum could not be supported. One would have to consider more seriously a meningococcal septicemia leading to adrenal failure. However, the duration of the disease (five days before admission and four days after) would be unusual. There was a five-day period without treatment during which the patient was ill but not so critically ill as patients with a combination of meningococcal septicemia and adrenal involvement. Again, the rash was surely not that ordinarily seen in meningococcal infection. I think the high fever, the cellular reaction in the blood and possibly the rash all suggest infection, but without any evidence of blood cultures or other studies it is impossible to say whether or not this patient had a septicemia. The rash with an apparently thin fluid in the vesicles, if related to infection, suggests a streptococcal infection.

Originally, I had thought of the possibility of a tumor involving the region of the kidney or adrenal gland but was unable to think of any condition that would involve so completely either both kidneys or both adrenal glands, so I have discarded that possibility.

In an attempt to summarize, I shall say that it is difficult to determine whether or not both adrenal and renal failure were present in this patient, but my choice, with the knowledge given here, is that there was an underlying renal disease and that the terminal uremia was precipitated by a superimposed infection. I find nothing to indicate the nature of the superimposed infection.

DR BERNARD JACOBSON: Was the rash caused by the penicillin?

DR ELLIS: That is what we wondered about when we first saw it. It became most apparent about 6:00 o'clock during the night before the patient died. We did not think it was any more than that which one sees in patients who have had a high fever for a long time.

DR ROPES: Can you explain the localization? You described it on the trunk and arms rather than generalized.

DR ELLIS: There is no explanation for that at all. But the striking feature about this patient when first seen was the cyanosis of the nails, duskeness of the lips, dry skin and hypotension. By the time he got to the hospital his motor activity was the thing that was very prominent and persisted until about 6:00 o'clock the night before he died. The urinary findings, the high nonprotein nitrogen and the relatively low specific gravity, in the face of the very marked dehydration, bothered us, as they did Dr Ropes. For the first twelve hours we thought that he had anuria, but when he was catheterized at the end of that time we obtained a large volume of urine, with a specific gravity of 1.010 to 1.012 and from that time on he voided quite freely and was incontinent. We were also bothered during the course of the illness by the persistently high fever and the persistent tachycardia. We believed as Dr Ropes did that the possibilities were adrenal insufficiency, renal insufficiency and infection. We were left with no other choice except to treat him as if he had adrenal insufficiency, and to treat infection, if he had one, with penicillin and try to get him back to a normal electrolyte balance. The treatment was given in detail in this abstract with the hope that we would have some discussion about it after the diagnosis was made. We believed at the time that the patient died that the clinical diagnosis was adrenal insufficiency. We were unable to get any proof that he had an infection although we tried hard and suspected that he might have meningococcal septicemia. Blood cultures were taken, and the last time I saw the record they were not recorded.

DR TRACY B. MALLORY: They remained negative.

#### CLINICAL DIAGNOSES

Acute adrenal insufficiency

Acute infection and septicemia (cause undetermined)

## DR ROPES'S DIAGNOSES

Renal disease (? glomerulonephritis)  
Terminal uremia  
Septicemia?

## ANATOMICAL DIAGNOSES

Primary atrophy of adrenal cortex  
Addison's disease  
Chronic thyroiditis, moderate  
Chronic hepatitis, nonspecific  
Persistent thymus

## PATHOLOGICAL DISCUSSION

DR MALLORY I do not know that we can explain the whole picture. The outstanding feature of the autopsy was atrophy of the adrenal glands. They were estimated to weigh between 2 and 3 gm., with little cortical tissue, what remained appeared to be chiefly medulla.

On microscopical examination we found scattered fragments of persistent cortex. The cells were very unusual in type. They were four or five times as large as normal and contained practically no lipid. A few did contain the normal pigment seen in the reticular layer. The cells were clumped in small nodules, with no orderly cord formation. Some clusters of lymphocytes were present.

There were no other significant gross findings at autopsy. The pituitary and thyroid glands, testes and parathyroid glands were grossly normal. The thymus was quite large, weighed 30 gm. and was evidently active, with very little involution. There was a terminal congestion and edema of the lung but no evidence of pneumonia. On microscopical examination the pituitary gland appeared normal, the thyroid gland showed moderately severe thyroiditis, with some degree of atrophy, the parathyroid glands were normal, and the testes showed a slight depression of activity. The early stages of spermatogenesis were present but mature spermatozoa were infrequent. But any patient near death can show that much depression of spermatogenesis.

One surprising microscopical finding was a considerable degree of lymphocytic infiltration of all the portal areas of the liver, but I do not know what to make of that. It did not look like infectious hepatitis. I have to leave it without explanation. It is beyond the normal limits.

DR ALFRED KRAVES Were the kidneys normal?

DR MALLORY Entirely — grossly and microscopically.

DR FULLER ALBRIGHT When I saw this man the problem was one of treatment. It had already been decided that he had Addison's disease. We did not know the cause of the Addison's disease. What about therapy? The question is whether we over-treat or undertreat these cases. I think that the

tendency is to overtreat them. The trouble is that there is no easy laboratory test that one can perform quickly and that parallels the patient's condition. Dr Robert Loeb,<sup>1</sup> of New York, has shown that a patient can die with a high fever and still have normal serum electrolytes. Some unknown factor is present that we do not know how to evaluate. I think, if anything, we overtreated this patient, the serum sodium was high — 150 milliequivalents per liter (the normal is equal to 140 milliequivalents per liter).

A word about the term "atrophy" — we divide cases of Addison's disease into two pathological groups: tuberculosis and something else, which is usually called atrophy. Is that right, Dr Mallory?

DR MALLORY Yes.

DR ALBRIGHT Does this agree entirely with other cases that you call atrophy?

DR MALLORY That is a difficult decision so far as I am concerned.

DR ALBRIGHT When I was in Vienna, Erdheim showed a case with this second kind of lesion. One adrenal gland was entirely gone, and half the other. He said that eventually the patient would have had Addison's disease when the second gland had become completely involved. This disease is very different from the atrophy that occurs when there is no pituitary stimulus to the adrenal cortex. That is real atrophy. This is something else. The cells disappear by some sort of necrosis, and the whole gland is not involved simultaneously. It is not my idea of atrophy. It is more analogous to thyroiditis.

DR MALLORY The problem that Dr Albright raises is essentially semantic, and I cannot solve it for him. "Atrophy" and "involution" both etymologically connote a comparatively slow shrinkage of tissue such as occurs with aging or with disease. Yet "atrophy" has been in accepted medical usage for over a century to describe fulminant necrosis of the liver. Friedman<sup>2</sup> in reporting a group of 26 cases of Addison's disease recently used the term "contraction," borrowed from the terminology of renal disease. I cannot see that it is an improvement. I do agree with Dr Albright that in this case there was active destruction of the adrenal cortex rather than the secondary atrophy seen in Simmonds's disease.

DR JACOBSON In these cases of cortical necrosis of the kidney in women, what is the adrenal picture?

DR MALLORY It may be normal. We have also seen cases in which the adrenal gland shows the same type of necrosis as the kidney, and hemorrhagic necrosis has been reported in the pituitary gland also.

## REFERENCES

1. Loeb, R. F. Disease of adrenal. In *Oxford Medical History*, Vol. 3, 1113 pp. New York: Oxford University Press, 1947. Pp. 21-504.
2. Friedman, N. D. Pathology of Addison's disease: adrenocortical contraction. *Am. J. Path.* 24:877, 1947.

# The New England Journal of Medicine

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## FEBRUARY MEETING OF THE COUNCIL

A STATED meeting of the Council of the Massachusetts Medical Society was held on February 4, 1948. Among the business, which was transacted with more than usual dispatch, the following items are of particular interest or importance.

The President, under the new arrangement between the Society and the Boston Medical Library, nominated the following to serve as trustees of the Library representing the Society: Dr. Curtis C. Tripp, of New Bedford, Dr. John J. Curley, of Leominster, Dr. Edward S. O'Keefe, of Lynn, and Dr. Albert Ehrenfried, of Brookline.

During consideration of the report of the Committee on Public Relations, discussion took place as to whether the Council should endorse the objectives of the National Physicians Committee, and a motion was offered to this effect. In view of the

fact that the Committee on Public Relations had appointed a subcommittee to meet with the Committee on Medical Economics and bring in a report on this matter to the Council, the motion was tabled.

Dr. John F. Conlin presented a general summary of his work as Director of Medical Information and Education, stressing the importance of public relations to individual physicians as well as to society at large. With reference to the woman's auxiliaries he reported that Norfolk and Suffolk are organized, with Essex South and Middlesex South well on the way. In April the districts that are organized will form a nucleus for the state auxiliary.

The report of the Committee on Cancer, asking for approval of the establishment of a cancer-detection clinic at the Palmer Memorial Hospital, was accepted, and the establishment of this clinic approved in principle. A similar request had been tabled at the October meeting of the Council. In this more comprehensive report it was explained that such a clinic would serve as a proving ground for different types of diagnostic methods and as a center where physicians might come to determine procedures applicable to the problems of their own practice.

The report of the Committee of Seven that had been appointed at the October meeting "to study the need for a full-time secretary and to define the duties of the Secretary, Director of Medical Information and Education, and the Executive Secretary of the Society" was accepted. This report recommended the employment of a full-time secretary and called for certain revisions in the by-laws of the Society that would implement the proposed changes.

Under suspension of rules, House Bill 104 introduced in the state legislature was approved. This bill designates the Massachusetts Department of Public Health as the agent, under the Federal Hospital Survey and Construction Act, to survey the hospital needs of the Commonwealth. Also under suspension of rules the Council adopted a resolution offered by Dr. Vlado A. Getting approving the turning over to the American Red Cross of the blood and blood-derivative program of the Commonwealth. The Red Cross voted in June, 1947, to assume this program, which has been conducted by

the Department of Public Health, on condition that the Massachusetts Medical Society approve in principle and serve, with the Department, in an advisory capacity

### THE RED CROSS NEEDS YOUR HELP

THE annual drive for the Greater Boston Red Cross Fund was launched at an opening rally held in Symphony Hall on February 25. The campaign will occupy the month of March. The Greater Boston share of the national goal of \$75,000,000 is \$1,440,000. These quotas have been increased from last year's goals of \$60,000,000 and \$1,280,000 respectively.

The increased sums of money sought reflect only the increased costs of human activities in general. The public is reminded that this year greater sums are needed for an equal job, despite greater emphasis on a peacetime program, the Red Cross is continuing and even expanding its work for veterans and their dependents.

Recounting past services of the Red Cross may help to remind us that they will be needed again and that this great humanitarian organization requires the nation's unflinching support.

During the past fiscal year nearly 100,000 persons received emergency help and rehabilitation in 312 disaster operations, in the first ten months of 1947 alone, disaster relief appropriations approximated \$9,500,000. Financial assistance to servicemen and veterans and their families amounted to \$11,944,365 for the year. To turn from dollars to hours, volunteer special services workers gave 25,000,000 of the latter.

In 1947 the American Red Cross recruited 2564 nurses to aid in the campaign against poliomyelitis. Red Cross public-health nurses made 351,600 visits, and 118,340 certificates for completion of home-nursing service courses were issued during the year. In retrospect it is a source of satisfaction to recall that 11,230,000 certificates of proficiency in first aid have been issued since that program was instituted in 1910, and that since the program to "waterproof" America was launched in 1914, the nation's drowning rate has been halved.

The Junior Red Cross of 19,270,811 members will ship a million boxes to children overseas during the current school year. 34 nations are participating in

the Junior Red Cross international school-correspondence program.

The national blood program, when completely organized, will make whole blood and its derivatives available without cost to all the people of our nation.

This is but a partial classification of the major activities of the Red Cross. To carry on with them and with its other commitments requires the continued support that has always so gladly been given.

### ROBERT NASON NYE MEMORIAL STUDY

THE Massachusetts Division of the American Cancer Society has voted a grant to the Massachusetts General Hospital of approximately \$2500 for a particular purpose. The sum thus appropriated represents the money so generously donated in memory of the late Dr. Robert N. Nye. The purpose is to initiate and at least partly support the Robert Nason Nye Memorial Study.

This study, a long-desired project of the X-ray Department of the Massachusetts General Hospital, where Dr. Nye served his internship, is concerned with the evaluation of changes in the peripheral blood correlated with known amounts of exposure to radiation sustained by the employees and staff of the X-ray Department. Among other matters to be studied is the incidence of leukemia among such workers.

The study will be under the supervision of Dr. Laurence L. Robbins, roentgenologist of the Hospital, with the assistance of Dr. Francis M. Hunter, of the Clinical Laboratory, and in consultation with Dr. John G. Trump, of the Massachusetts Institute of Technology.

### MASSACHUSETTS MEDICAL SOCIETY

#### BLUE CROSS ENROLLMENT

The following letter explains the present situation regarding enrollment in Blue Cross of members of the Massachusetts Medical Society. Blue Cross has already discontinued the practice of allowing enrollments on the first of each month and adopted the policy of permitting them only once a year at the time of a general reopening for all nonsubscribing members. August had been suggested as a convenient month for this reopening.

II QUIMBY GALLUPE  
Secretary

February 6, 1948

Mr Robert St. B. Boyd, Executive Secretary  
Massachusetts Medical Society  
8 Fenway  
Boston 15, Massachusetts  
Dear Mr Boyd

I regret to state now that it is impossible for me to tell you whether or not August may be the re-opening date for your group and it is difficult for me to say at this time whether or not there will be another opportunity for members of the Medical Society to join the Blue Cross Plan

Please understand that this is due only to a complete change in our methods of enrollment and every effort is going to be made to satisfy groups such as yours which were enrolled on Direct Payment. I have taken this matter up with Mr Cunningham and he has told me that your group will be discussed shortly as to whether re-openings will be allowed in such groups

Please be advised that as soon as possible I will let you know whether or not your group may be re-opened, if so, what month will be preferable and also the necessary number of applicants to be secured at that time

I am sorry that I am not in a position to give you complete information for presentation in your *Journal* as I know that was your desire but you will realize that we are in a very difficult position at this particular time due to the high incidence of hospitalization and the many changes now being made of necessity have left us with many unsolved problems

I will notify you just as soon as possible

JOHN H McLAUGHLIN  
Enrollment Representative

Massachusetts Hospital Service Inc  
Massachusetts Medical Service  
38 Chauncy Street  
Boston

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATHS

CHENEY — Harry A. Cheney, M.D., of Campton, died on July 15. He was in his seventy-seventh year.

Dr. Cheney received his degree from University of Vermont College of Medicine in 1894. He was a member of the staff of the Scoville Memorial Hospital in Plymouth.

HUCKINS — Thion H. Huckins, M.D., of Tilton, died on January 3. He was in his seventy-fifth year.

Dr. Huckins received his degree from Dartmouth Medical School in 1902. He was a member of the staff of Franklin Hospital.

His widow, a son and a brother survive.

SULLIVAN — Daniel J. Sullivan, M.D., of Manchester, died on December 16. He was in his fifty-sixth year.

Dr. Sullivan received his degree from Tufts College Medical School in 1916. He was formerly chief of the surgical staff of Sacred Heart Hospital and surgeon on the staff of Hillsborough County General Hospital. He was secretary of the New England Regional Committee of Fractures and was a fellow of the American Medical Association.

His widow, two sons, two daughters and a sister survive.

## A HUNDRED YEARS AGO

The Counsellors of the Mass Medical Society will meet at their rooms in the Masonic Temple, Tremont st., at 11 o'clock in the morning of February 2. Business matters of peculiar interest will be acted upon, and it is therefore desirable that gentlemen should be in their seats at the specified hour. — A melancholy interest is connected with the sudden and suicidal death of Dr. Horace Wells, from the circumstance of his

name being associated with the discovery of the inhalation of gases to overcome consciousness in surgical operations. He labored incessantly to establish his claim to the honor of discovery, and certainly produced a mass of testimony that convinced many that his researches, experiments, and suggestions influenced others to proceed in a course of investigation, that finally led to the triumphant discovery of the anaesthetic properties of sulphuric ether, and subsequently, under the clear-sighted exertions of Dr. Simpson, of Edinburgh, of the same surprising qualities in chloroform. — Messrs W. B. Little and Co., Hanover street, Boston, are manufacturing this new agent in large quantities. Much of it is packed up in phials small enough to be carried in a vest pocket, and secured at the cork in a manner to prevent loss by evaporation. Dr. C. T. Jackson, the chemist, whose reputation is as extensive as the boundaries of Science, speaks with entire confidence of the purity and excellence of Mr. Little's chloroform for all the purposes for which it may be required. The demand for it almost exceeds belief — and we are almost disposed to ask under what circumstances it can all be used. — A bill has been before the legislature of New York, which proposes a fine of \$25 for selling adulterated drugs and medicines, if known to be such, and the same fine where the ingredients of a compound are not stated on the label, in legible English, but it was finally lost by a decisive vote. — 140 students are in attendance on the Medical lectures in Harvard University, the present season. — At Bellevue Hospital, out of 600 patients there are said to be over 200 of Typhus Fever, while three of the Assistant Physicians are sick of the fever, and two others but just recovering from an attack. — Extracted from the *Boston Medical and Surgical Journal*, February, 1848.

R. F.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### THE COMMONWEALTH'S RHEUMATIC-FEVER PROGRAM

Several hundreds of children in Massachusetts are victims of rheumatic fever each year. Some of these children will be crippled or handicapped by this disease, others, without actual cardiac damage from a first attack, will need protection from further attacks. The second group is particularly important in the field of preventive medicine, and efforts should be directed toward provision of the most healthful living conditions possible. General health supervision and regular medical examinations will help to forestall the development of the more serious infections.

Another important part of a rheumatic-fever program is to make a definite diagnosis of the child

who has questionable heart disease and to interpret to the family just what degree of activity is possible. Unnecessary limitation of a child's life may be as detrimental to his future as too great physical effort. His possibilities as a self-supporting and useful citizen should be considered in any plan for care and aid to the child with rheumatic heart disease.

The Massachusetts Rheumatic Fever Program is offering in the Northeastern Health District diagnostic and consultative service, as well as complete clinic care, follow-up study and hospitalization when needed, for patients under twenty-one years of age. Further information and application blanks can be obtained from the District Health Office, 367 Main Street, Wakefield (Telephone, CRystal 9-1118).

## MISCELLANY

### NOTE

The following appointments to the teaching staff of Harvard Medical School were recently announced: Keith Merrill Jr., of Herndon, Virginia (A.B. Yale University 1940, M.D. Harvard University 1944), research fellow in surgery; Peter Howard Nash of Kent England (B.A. Cambridge 1938, M.A. Cambridge 1945, M.B.B.Chir. Cambridge 1941, D.P.H. London 1947), research fellow in medicine; John Robertson Sinton, of London England (M.B., B.Surg. London University 1944, M.R.C.P. Royal College of Physicians of London 1946), research fellow in medicine; Robert John Walsh, of New South Wales, Australia (M.B. University of Sydney 1939, B.S. University of Sydney 1939), research fellow in medicine; Daniel Sumner Ellis, of Cambridge (M.D. Harvard University 1939), assistant in medicine; William Burton Ayre, of Montreal, Canada (B.A. University of Alberta 1938, M.D. University of Alberta 1943), research fellow in medicine; Donald Harting of Cambridge (S.B. Harvard University 1945, M.D. Harvard University 1946), research fellow in pediatrics; Lytt Irvine Gardner of Cambridge (A.B. University of North Carolina 1938, M.A. University of North Carolina 1940, M.D. Harvard University 1945), research fellow in pediatrics; and John Martin Weller, of Oak Park, Illinois (A.B. University of Michigan 1940, M.D. Harvard University 1943), teaching fellow in biologic chemistry.

## NEW MEDICAL DIRECTOR UNITED STATES VETERANS ADMINISTRATION

Dr. Paul B. Magnuson, prominent orthopedic surgeon and closely identified with the reorganization of medical care in Veterans Administration hospitals, has been named chief medical director for the United States Veterans Administration.

Dr. Magnuson, former professor of surgery and chairman of the Department of Bone and Joint Surgery at Northwestern University Medical School, succeeds Dr. Paul R. Hawley who resigned on January 1 as medical chief and who now is serving as special assistant and adviser on medical problems.

## NEW YORK TUBERCULOSIS AND HEALTH ASSOCIATION

Dr. Kendall Emerson was elected president of the New York Tuberculosis and Health Association at the annual meeting held in the Association's headquarters, 386 Fourth Avenue, Manhattan, on January 27. All other officers were re-elected and two new members were elected to the Board of Directors.

The new Board members are Dr. Norman Plummer, medical director of the New York Telephone Company, and Dr. William Hunter Stearns, associate visiting physician, Chest

Service, Bellevue Hospital and instructor in medicine, College of Physicians and Surgeons, Columbia University.

Dr. Emerson, who was a charter member of the American College of Surgeons, was managing director of the National Tuberculosis Association for nineteen years until his retirement on December 31, 1947. He began his career as an orthopedic and general surgeon in Worcester, Massachusetts, and from 1923 to 1928 was chief of surgical services in the Worcester Memorial Hospital. In World War I he served with the British forces in the Royal Army Medical Corps from 1916 to 1918 and with the United States Army Medical Corps from 1918 to 1919. He was deputy commissioner and medical director for Europe for the American Red Cross during 1920-1921.

The annual health conference of the Association will be held in the Hotel Pennsylvania, New York City, on March 9.

## LASKER FOUNDATION AWARD

Dr. John Rock, of Boston, received on January 27, 1948, the Lasker Foundation Award and medal from the Planned Parenthood Federation of America. The award was made because of his investigations into the causes and cure of sterility.

## NATIONAL BLOOD PROGRAM

The American Red Cross has announced the appointment of Dr. Louis K. Diamond, assistant professor of pediatrics at Harvard Medical School, as technical director of the National Blood Program. Dr. Diamond is also director of the Boston Children's Hospital Blood Bank and Research Laboratory, director of the Blood Grouping Laboratory of Boston and consultant in pediatric hematology at the Massachusetts General Hospital.

The most recently opened donor center in the \$10,000,000 chain has been established at Stockton, California.

## EFFECT OF WAR ON CHILDREN

Award of a \$20,000 research grant to the International Committee on Mental Hygiene under the National Mental Health Act was recently announced.

The grant will be used under the direction of Dr. David Levy, professor of psychiatry, Columbia University College of Physicians and Surgeons, for a study of the effect of war on children. It will be presented at the International Congress on Mental Health, to be held in London in August.

## MENTAL HEALTH CLINIC

The first United States Public Health Service demonstration mental health clinic has been opened in Prince Georges County, Maryland. The clinic will be operated jointly by the Maryland State Department of Health and the Public Health Service, with federal funds under the National Mental Health Act. Forty thousand dollars has been appropriated for the fiscal year 1948.

The clinic is under the direction of Dr. Mabel Ross, child psychiatrist formerly with the Johns Hopkins Hospital. Psychiatric service is offered to all residents of Prince Georges County, which has a population of 140,000.

## CORRESPONDENCE

### OLD SPANISH SWINDLE IN NEW FORM

To the Editor: A communication from the acting Inspector in charge, Post Office Department, Boston, is transmitted herewith for publication in the *Journal* since the fraud described applies to physicians as well as to dentists and members of other professions. The letter is as follows:

The following information is respectfully offered as material for inclusion in a forthcoming issue of the *New England Journal of Medicine*.

Tennison Jefferson, post office Inspector in charge, Boston, estimates that over a thousand Spanish prisoner swindle letters have been mailed recently at Mexico City, Mexico, addressed to doctors, dentists and others through-



out New England. The operators of the revived swindle appear to be using names and addresses selected from publications such as *Who's Who in America* and those listing the names of doctors and dentists.

Jefferson, who has personally investigated most of the major foreign lotteries and frauds during the past decade, explained that these prisoner letters are allegedly mailed by a man imprisoned in Mexico for bankruptcy. The prisoner states in his letter that he needs only a few thousand dollars to lift an embargo on his trunk, containing \$375,000.00 in United States currency and held in a customhouse in the United States. One third of this money, or \$125,000.00, is offered to the addressee of the letter if he will come to Mexico with \$2,000.00 in cash to aid the prisoner. As evidence of good faith the prisoner also offers to place his "dear daughter" under the protection of the man to whom the letter is addressed.

He described the swindle as one of the oldest in existence, having originated in Spain many years ago. Its headquarters were moved to Mexico around 1900. Information furnished to the Post Office Inspection Service shows that many old family archives contain Spanish-prisoner letters received before the turn of the present century. Jefferson remarked, "Incredible as it may seem, during the years that this swindle has operated the number of Americans gullible enough to respond with cash to its promise of easy money has been sufficient to keep it alive. These swindlers are currently seeking a new crop of post war victims."

Inspector in Charge Jefferson requests those who receive Spanish prisoner letters to mail or bring them promptly to his office in the Federal Building, Boston, so that United States mail addressed to the swindlers may be identified therefrom and held under postal fraud orders.

A G LAGACE  
*Acting Inspector in Charge*

Inspection Service  
Post Office Department  
Boston Division

H QUIMBY GALLUPE, M D  
*Secretary*

Massachusetts Medical Society

## NOTICES

### ANNOUNCEMENT

Drs Edward L. Young, Walter E. Garrey, Walter E. Wilson, Jr., and Howard M. Trafton announce the removal of their offices to 1180 Beacon Street, Brookline.

### HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, March 9. A symposium on virus diseases will be presented.

#### PROGRAM

##### Afternoon (4 30 to 6 30)

Max Bovarnick, M D. Chemical Nature of the Virus Receptors in Red Cells

John C. Snyder, M D. Chemotherapy of Rickettsial Diseases

Herbert R. Morgan, M D. Experiments on Chemotherapy with Agents of the Psittacosis Lymphogranuloma Group

Charles A. Janeway, M D. The Effect of M-casles on the Nephrotic Syndrome

##### Supper in Vanderbilt Hall at 6 30 p m

##### Evening (8 00 to 10 00)

John F. Enders, Ph D. Mumps

Maxwell Finland, M D. Influenza

F S Cheever, M D. Epidemic Diarrhea of Suckling Mice

Robert Rustigian, Ph D. Studies on Immunity of Theiler's Virus

Subsequent meetings will be held on April 13 and May 11

### NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, on Tuesday, March 9, at 8 p m. Dr. Ralph M. Tovell's group will present the following program:

The Physiologic Basis for Resuscitation of the Newborn  
Dr. David M. Little, Jr.

Cardiovascular Collapse During Subarachnoid Block  
Recovery following administration of procaine.  
Dr. Robert R. Cross

Treatment of Cardiovascular Emergencies during Anesthesia  
Case report.  
Dr. Harvey F. Dritz

Proved Ventricular Fibrillation during General Anesthesia with Complete Recovery.  
Dr. R. Starr Lampson

Physicians and medical students are also invited to attend a meeting of the Anesthesia Study Commission to be held at Boston University School of Medicine on Tuesday, March 30, at 8 p m. Three interesting cases are to be presented. Guest discussants will review the cases.

### AMERICAN HOSPITAL ASSOCIATION

The fiftieth-anniversary convention of the American Hospital Association will be held in Atlantic City, New Jersey, from September 20 to 23, with headquarters at the Traymore Hotel and with meetings and exhibits at the Atlantic City Convention Hall.

The program, which is devoted to the subject "Hospitals — Vital to Better Living," will consist of morning and afternoon sessions concerned with important issues and problems of the care of patients and of hospital finances, as well as the role of the hospital in community life and the challenge to hospitals. Special events will include the sessions of the House of Delegates, an informal reception followed by a buffet dinner and the annual banquet. Commercial and educational exhibits will be conducted.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 4

##### THURSDAY, MARCH 4

12 00 p m. Clinicopathological Conference. Nurses Home Allerton Hospital, Brookline.

##### FRIDAY, MARCH 5

\*10 00 a m.—12 00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

##### MONDAY, MARCH 8

12 00 m. Clinicopathological Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

\*12 15—1 15 p m. Clinicopathological Conference. Peter Bent Brigham Hospital.

##### TUESDAY, MARCH 9

\*12 15—1 15 p m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

\*1 30—2 30 p m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

4 30 p m. Harvard Medical Society. Amphitheater of Building D, Harvard Medical School.

8 00 p m. New England Society of Anesthesiologists. Bigelow Amphitheater of the White Building, Massachusetts General Hospital.

##### WEDNESDAY, MARCH 10

\*12 00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

\*2 00—3 00 p m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater. Children's Hospital.

\*Open to the medical profession.

JANUARY-APRIL. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

MARCH 1. New England Heart Association. Page 278, issue of February 19.

MARCH 9. Harvard Medical Society. Notice above.

MARCH 9. New England Society of Anesthesiologists. Notice above.

(Notices continued on page xv)

## NOTICES (Concluded from page 310)

- MARCH 9. New York Tuberculosis and Health Association. Page 136. Issue of January 72.
- MARCH 11. Diagnosis and Treatment of Painless Jaundice. Dr. Chester M. Jones. Festschrift Association of Physicians. 8:50 p.m. Harvard Hall.
- MARCH 11. Fiftieth Anniversary of Cornell University Medical College. Page 136, Issue of January 72.
- MARCH 12 and 13. American Association of Pathologists and Bacteriologists. Page 204. Issue of February 5.
- MARCH 28-APRIL 4. American Association of Industrial Physicians and Surgeons. American Industrial Hygiene Association. American Conference of Governmental Industrial Hygienists. American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler Boston.
- APRIL 7, 9, 14 and 16. American Trudeau Society. Page 240. Issue of February 12.
- APRIL 19-23. American College of Physicians. Page 241, Issue of July 31.
- APRIL 29-MAY 2. American Academy of Pediatrics. Page 240. Issue of February 12.
- MAY 6-8. American Association for the Study of Gonorrhea. Page 241, Issue of July 31.
- MAY 16-23. International College of Surgeons. Page 136. Issue of January 22.
- MAY 17-20. American Urological Association. Hotel Statler Boston.
- MAY 18-22. American Association on Mental Deficiency. Copley Plaza Hotel Boston.
- MAY 20-25. American Board of Ophthalmology. Page 10. Issue of January 29.
- MAY 25-27. Massachusetts Medical Society. Annual Meeting. Hotel Statler Boston.
- JUNE 28-30. American Academy of Pediatrics. Hotel Schroeder Milwaukee Wisconsin.
- JULY 12-17. First International Poliomyelitis Conference. Page 36. Issue of January 1.
- SEPTEMBER 13-15. American Academy of Pediatrics. Olympic Hotel Seattle Washington.
- SEPTEMBER 30. American Hospital Association. Page 310.
- SEPTEMBER 29. Mississippi Valley Medical Editors Association. Page 170. Issue of January 29.
- OCTOBER 6-9. American Board of Ophthalmology. Page 170. Issue of January 29.
- NOVEMBER 20-23. American Academy of Pediatrics. Annual Meeting. Chilton Haddon Hall Hotel Atlantic City New Jersey.

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

- MARCH 9. Franklin County Hospital Greenfield.
- MARCH 11. Annual Meeting. Hotel Weldon Greenfield.

## MIDDLESEX EAST

- MARCH 14.
- MAY 12. Annual Meeting.
- Meetings will be held at the Bear Hill Golf Club Wakefield.

## NORFOLK

- MARCH 23. Harvard Night.

## PLYMOUTH

- MARCH 18. Goddard Hospital Brockton.
- APRIL 13. State Farm, Bridgewater.
- MAY 20. Lakeville Sanatorium Lakeville.

## WORCESTER

- MARCH 10. Memorial Hospital, Worcester.
- APRIL 14. Worcester Rahnemann Hospital.
- MAY 12. Annual Meeting.

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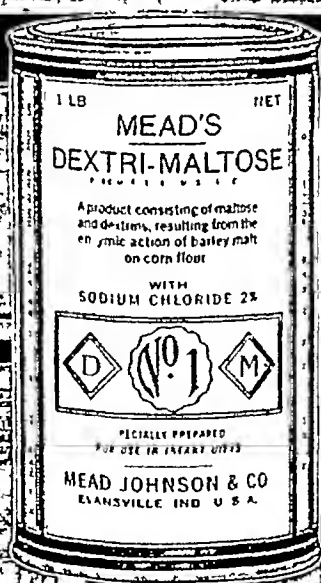
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## THE OCCURRENCE OF EXTENSOR SPASM IN PATIENTS WITH COMPLETE TRANSECTION OF THE SPINAL CORD\*

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LONG survival of patients with complete severance of the spinal cord is rarely encountered in civilian life. During the recent world conflict, however, the high incidence of casualties from high-explosive missiles resulted in a moderate number of such injuries. The medical and surgical advances of recent years, together with rapid and efficient evacuation from the field of battle, have greatly increased the initial survival rates of these men. Paraplegia centers established during the war employed new techniques of bladder management, assiduous hospital care and careful medical and physical rehabilitation. These and other factors combined to increase markedly individual and group longevity as compared with the average life span of patients suffering similar injuries during World War I. Coincidentally, an opportunity was provided for the study of an unprecedented number of traumatic lesions of the spinal cord.

This article represents an abbreviated report of observations relating to certain patterns of involuntary activity exhibited by long-surviving patients with complete severance of the spinal cord. A detailed account of these studies is in preparation. The findings seemed of sufficient theoretical and practical significance, however, to warrant publication of a preliminary report.

Heretofore, it has generally been assumed that after recovery from spinal shock, the only patterns of involuntary activity in skeletal muscle groups exhibited by patients with complete severance of the cord are flexor spasms of the lower extremities and the mass reflex—that is, severe flexor spasm accompanied by spinal sweating and certain visceral manifestations. This assumption rests almost entirely upon the work of Head and Riddoch,<sup>1,2</sup> who, in 1917, conducted an intensive study of 8 patients with ver-

sified, anatomic transections of the cord and of numerous other patients with partial cord lesions. Head and Riddoch reported that, in direct contrast to the totally transected group, patients with partial cord damage exhibited exaggerated extensor movements.

Since the publication of this classic study, one of the principal criteria for the establishment of a diagnosis of complete division of the cord has been the absence of extensor spasm in muscle groups below the level of transection. This criterion has been accepted as an all-or-none rule by many neurologists. Fulton<sup>3</sup> makes the following statement:

Instances of spinal paraplegia are seen with complete loss of sensibility below the level of the lesion and yet may have marked extensor spasm if the limbs are manipulated, especially if the leg is elevated from the popliteal space. This is an *unfailing sign of an incompletely divided cord* and may be of value both in diagnosis and prognosis.

Russell Brain<sup>4</sup> endorses the theory that extensor hypertonia depends upon the integrity of the vestibulospinal tracts and that destruction of the latter results in a dominant flexor reflex. "After a traumatic lesion, causing immediate and complete severance of the cord, paraplegia-in-extension never occurs, because the vestibulospinal tract is interrupted from the beginning and as soon as the stage of spinal shock has passed, paraplegia-in-flexion develops." Similar statements are to be found in most neurologic texts.<sup>5-7</sup>

On the Paraplegia Service of the Cushing Veterans Administration Hospital, we have had the opportunity of studying 27 verified cases of complete transection of the spinal cord in white men. The levels of transection ranged from the second to the twelfth dorsal vertebrae. In every case complete examinations could be made two or more years after transection. In 2 men the pattern of involuntary activity in muscle groups below the transected level consisted of flexor spasms alone. Two men exhibited approximately equal flexor and extensor spasms and 19 showed predominant extensor spasms with flexor components. In no patient was extensor spasm alone elicited. Five men were completely

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†The views expressed in this article are those of the authors and do not necessarily represent those of the Veterans Administration.

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flaccid, and no reflex activity was noted in the musculature innervated below the level of cord section

The following case illustrates a typical progression of reflex activity

CASE 2 J Z, a 22-year-old man, sustained multiple machine-gun wounds on February 3, 1945. He was immediately paralyzed from the level of the nipples downward. X-ray study disclosed compound, comminuted fractures of the second and third dorsal vertebrae and evidence of fragmentation of the neural canal at that level. Exploratory laminectomy on December 4, 1946, revealed a complete

being converted into a rigid pillar. Rigidity of the adductor musculature was a prominent feature of this picture.

Noiceptive stimulation of the plantar and genital areas elicited dorsiflexion of the four toes, with no movements of the hallux, moderate dorsiflexion of the foot and sharp, tugging flexion at the knee and pelvis. Crossed phenomena included plantar flexion of the foot and visible tightening of the anterior and posterior thigh musculature. The abdominal wall was not involved in the flexion reflex. The right lower extremity failed to demonstrate full triple flexion, but was considerably stronger in extensor manifestations than the left.

The superficial abdominal reflexes were absent, and the deep ones were ++ in all quadrants. The knee jerk was ++++ on the right with sustained patellar clonus and

TABLE 1 *Manifestations of Reflex Activity in 27 Patients with Complete Severance of the Spinal Cord*

LEVEL OF LESION	CASE NO	INVOLUNTARY MOVEMENT FIRST NOTED	STEPPING MOVEMENTS	SCISSORING MOVEMENTS	CROSSED PHENOMENA
D2	1	Flexion	Present	Present	Present
	4	Flexion	Absent	Present	Present
D3	2	Flexion	Present	Present	Present
	3	Flexion	Present	Present	Present
	5	None	Absent	Absent	Absent
	7	Flexion	Present	Present	Present
D4	6	Flexion	Present	Present	Present
	8	None	Absent	Absent	Absent
D5	9	Flexion	Absent	Present	Absent
	10	Flexion	Present	Present	Present
	11	Flexion	Present	Present	Present
	12	None	Absent	Absent	Absent
D6	13	Flexion	Present	Present	Present
	14	Flexion	Present	Present	Present
	15	Flexion	Absent	Present	Present
	16	None	Absent	Absent	Absent
D7	17	Flexion	Absent	Present	Absent
D8	18	Flexion	Present	Present	Present
	19	Flexion	Present	Present	Present
D9	20	Flexion	Absent	Present	Present
	22	Flexion	Present	Present	Present
	23	Flexion	Present	Present	Present
D10	21	Flexion	Present	Present	Present
	24	Flexion	Absent	Present	Present
	25	Flexion	Present	Present	Present
D12	26	None	Absent	Absent	Absent
	27	Flexion	Absent	Present	Present

anatomic severance of the spinal cord with a gap between the scarred ends

Involuntary movements of the lower extremities were first noted 20 days after injury, when "someone pulled the hairs along my right thigh and the leg jumped." Bilateral flexor spasms gradually manifested themselves and within 6 months had become quite frequent and vigorous. It became necessary to tie the patient to his bed as a safety measure. Occasional extensor spasm occurred, but it was not until 18 months after injury that the strength and frequency of extension increased. Stepping movements were noted, and sudden over-all rigidity stiffened him out on the bed or slid him out of his wheel chair. Penile erections have occurred frequently since injury, but ejaculation has never been noted.

Neurologic examinations 2 years and 2 months after injury disclosed that extensor spasm, although not precipitated by plantar stimuli, became manifest immediately if the thighs were stroked or squeezed, if pressure were applied at the popliteal region, or if the patient were shifted from a sitting to a supine position. Rigidity was generalized from the level of the xiphoid process caudad and was sustained for approximately 5 seconds. If one lower extremity were elevated by lifting at the popliteal space, initial ipsilateral extension occurred and frequently crossed to the opposite extremity. Rapid lowering of an extended leg evoked severe ipsilateral extensor stiffening, which was invariably crossed. The resultant reflex figure consisted of bilateral extension of the lower extremities, the entire body below the level of transection

+++ on the left. Elicitation of patellar clonus on the left frequently resulted in sustained extensor rigidity of that extremity. Ankle jerks were ++ bilaterally with sustained clonus. Babinski's sign could not be elicited.

## DISCUSSION

An unparalleled opportunity for the study of long-surviving patients with traumatic lesions of the spinal cord has been afforded by World War II, and knowledge of the reflex functions of the cord has recently been further clarified. For example, earlier views regarding the physiology of the "automatic" bladder have been re-evaluated,<sup>7-9</sup> and hitherto unknown facts concerning the sensory capacities of the isolated spinal cord have been reported.<sup>10</sup> It is not surprising, therefore, that an exhaustive study of the reflex patterns exhibited by patients with complete spinal-cord transection reveal data that conflict with previous observations.

Release of the vestibulospinal tracts from suprasegmental control (with a resultant uninhibited flow

of impulses to the extensor muscles) provides a rational explanation for the extensor spasms that may predominate after partial lesions of the spinal cord. It might appear logical to assume the corollary of this hypothesis to be true that complete interruption of the vestibulospinal tracts precludes the occurrence of extensor spasm below the level of the lesion. The preceding case studies are not in agreement with such a hypothesis, however, for it is evident that quite marked extensor patterns may

## SUMMARY

The involuntary-activity patterns of skeletal muscles below the level of the lesion in 27 verified cases of complete spinal-cord transection have been studied. In each case examination was possible at least two years after division of the cord had occurred.

Two patients exhibited flexor spasms alone, 2 showed approximately equal flexor and extensor spasms, and 19 displayed predominant extensor

TABLE 1 (Continued)

LEVEL OF LESION	CASE No.	TRIGGER AREAS FOR EXTENSOR SPASM	DELT	DOOR REFLEXES	BABINSKI REFLEX	DOMINANT SPASM PATTERN AFTER TWO YEARS
		ON DIRECT MECHANICAL STIMULATION				
D2	1	Thigh popliteal space	Body legs	1 creased	Present	Extension
D3	2	Plantar surface, popliteal space, thighs	Body legs	1 creased	Present	Extension
	3	Thigh popliteal space	Body	1 creased	Present	Extension
	5	Thighs	Body legs	1 creased	Absent	Flaccid
D4	6	Plantar surface popliteal space, thighs	Body legs	Increased	Present	Extension
	8			Absent	Absent	Flaccid
D5	9	Thighs, popliteal space	Body legs	1 creased	Absent	Flexion
	10	Thighs popliteal space	Body legs	1 creased	Present	Extension
	11			1 creased	Present	Extension
	12			Absent	Absent	Flaccid
D6	13	Thighs popliteal space	Body	1 creased	Present	Extension
	14	Thighs popliteal space	Body	1 creased	Absent	Extension
	15		Body	1 creased	Absent	Extension
	16			Absent	Absent	Flaccid
D7	17			Normal	Present	Flexion
D8	18	Plantar surface thighs, popliteal space	Body legs	1 creased	Absent	Extension
	19	Thighs	Body	1 creased	Present	Equal flexion and extension
D9	20	Thighs, popliteal space	Body legs	1 creased	Present	Extension
	22	Thighs	Body legs	1 creased	Present	Extension
	23	Plantar surface thighs, popliteal space	Legs	1 creased	Present	Extension
D10	21	Thighs	Body	Increased	Present	Extension
	24	Thighs	Body legs	Present	Present	Extension
	25	Thighs	Body	Increased	Present	Equal flexion and extension
	26			Absent	Absent	Flaccid
D12	27	Thighs	Body	Increased	Present	Extension

predominate in subjects with complete division of the spinal cord. In our experience, the most typical sequence of events following cord transection is spinal shock, gradual return of reflex activity, flexor spasm, alternating flexor and extensor spasm, and finally, predominant extensor spasm. Fortunately, severe spasticity of the skeletal musculature can be completely eliminated, in most cases, by anterior rhizotomy.<sup>11</sup> It is probable that the discrepancies between our findings and those of earlier investigators can best be explained by the better physical condition and increased duration of life of present-day patients with complete spinal-cord transection.\*

\*The explanation of the primary extensor manifestations in these patients is not clear. We believe that such reflex responses represent the appearance of primitive, poorly integrated postural activity mediated through the isolated cord, in sharp contrast to the exclusively flexor responses which characterize the early stages of recovery after cord transection and which belong to Sherrington's<sup>12</sup> group of primitive nucleospinal reflexes. It appears that the functional capacity of the isolated cord, if given sufficient time to recover, is greater than has been assumed. An analogy may be drawn to earlier views concerning the capacities of mesencephalic and bulbospinal animals. Recently additional fighting and postural patterns have been demonstrated in these preparations because for the first time it has been possible to maintain them under satisfactory conditions for long periods.<sup>13,14</sup>

spasm with flexor components. Five patients showed complete flaccidity below the level of the lesion.

It is concluded that, although a patient with a complete spinal lesion passes through a period in which flexion reflexes alone are active, he frequently progresses to a stage of activity characterized by predominantly extensor reflexes, amounting in many cases to extensor spasm.

It is evident, therefore, that extensor spasm in skeletal muscles, innervated below the level of transection, is not conclusive proof of an incomplete division of the human spinal cord.

We are indebted to Dr. Donald Munro, consultant in neurosurgery, who has been a source of constant encouragement in the investigation and rehabilitation of the patients studied.

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## FATAL ACUTE PANCYTOPENIA FOLLOWING TRIDIONE TREATMENT\*

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TRIDIONE, since first proposed in 1945 as an anticonvulsant agent, has been generally accepted for the control of petit-mal and major psychomotor attacks. The favor it met with was justified by a number of reports, all claiming the efficiency of the drug in the control of convulsive disorders

and the apparent absence of toxic manifestations. No side effects were seen by Everett and Richards<sup>1</sup> in a large series of animals, including mice, guinea pigs, cats and rabbits, in which the anticonvulsant properties of the new drug were compared with those of Dilantin and phenobarbital, no toxic manifestations were found by Richards and Perlstein<sup>2</sup> in their series of human patients.

TABLE 1 Clinical and Laboratory Data

DAY OF DISEASE	TEMPERATURE	PULSE	RESPIRATIONS	BLOOD PRESSURE	RED CELL COUNT	WHITE-CELL COUNT	HEMO GLOBIN	PLATELETS	SEGMENTED FORMS	LYMPHOCYTES	MONOCYTES
	°F				x10 <sup>6</sup>	x10 <sup>3</sup>	gm/100 cc		%	%	%
1	102-103	80-100	18-20	130/80	2.33	1.60	10.5	6000	4	90	6
2	101-103	99-108	20	—	3.10	2.60	9.5	5000	1	99	—
3	101-103	90-110	20	—	3.05	1.85	11.5	5000	1	98	1
4	101-103	80-128	20-24	120/70	—	1.90	—	—	1	97	1
5	102-105	90-120	20-27	120/65	3.65	1.00	13.0	3000	—	100	—
6	100-103	80	32-60	—	—	—	—	—	—	—	—

and the apparent absence of toxic manifestations. No side effects were seen by Everett and Richards<sup>1</sup> in a large series of animals, including mice, guinea pigs, cats and rabbits, in which the anticonvulsant properties of the new drug were compared with those of Dilantin and phenobarbital, no toxic manifestations were found by Richards and Perlstein<sup>2</sup> in their series of human patients.

The first mention of side effects was made by Lennox,<sup>3</sup> who noticed skin rashes and hemeralopia in some of his cases. This was confirmed by DeJong,<sup>4</sup> who in addition called attention to occasional nausea, drowsiness and a sensation of lightheadedness. These toxic manifestations were considered to be relatively unimportant and not of the nature to justify excessive precaution in the administration of the drug.

The first fatal case of acute aplastic anemia following combined treatment with tridione and hydanto-

in was reported in 1946 by Harrison, Johnson and Ayer.<sup>5</sup> There was a strong suggestion in this case that one or both of these drugs had been instrumental in the development of the blood condition, but it was only after a similar case had been published by Mackay and Gottstein<sup>6</sup> that tridione was re-

garded as the determining factor in the fatal outcome in both cases. The course of events compared exactly in the 2 cases. In the case report of Harrison, Johnson and Ayer<sup>5</sup> a sixteen-year-old girl concurrently treated for a period of six months with tridione and methylphenylethyl hydantoin, began to show increasing pallor, accompanied by a tendency to bruise easily and by the appearance of petechial hemorrhages and ecchymotic areas in the skin. The essential laboratory findings were those of an increasingly severe pancytopenia. None of the agents generally used to stimulate hematopoiesis, including pentnucleotide, crude liver extract, folic acid and transfusions of blood, proved to be of any avail, and the patient died of uncontrollable menorrhagia on the thirty-eighth hospital day. A post-mortem examination confirmed the diagnosis of aplastic anemia. It was estimated that the bone marrow was reduced to a fourth of its presumed normal amount. Foci of hematopoiesis were present in the spleen and in the lymph nodes.

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In the case presented by Mackay and Gottstein,<sup>6</sup> in a twenty-four-year-old woman, evidence of the hematic crisis was delayed but abrupt, ten months after the use of a concurrent treatment with phenobarbital and tridione. Sixteen days after the onset, characterized by headache, weakness and fatigue, the patient died with a typical picture of aplastic anemia that no treatment was able to control. Autopsy revealed extensive hemorrhages throughout the body.

The third fatal case so far reported after tridione treatment occurred in this hospital. A brief report is presented below to emphasize further the hazards that the treatment involves and to offer some suggestions regarding the precautionary measures that must be followed if the use of the drug has to be continued.

### CASE REPORT

G. L., a 19-year-old girl, had been well until the age of 14 years when she developed sudden brief episodes of amnesia that occurred irregularly at intervals of days or months and lasted from a few seconds to a minute. These spells were consistently preceded by an aura, which consisted of flushing or of a tingling sensation of the face. Loss of consciousness, convulsions, falls, tongue biting and incontinence never occurred. On September 26, 1946, the patient was seen by a psychiatrist. Complete physical and neurologic examination

gingival mucosa did not appear to be abnormal. The temperature was 102 F.

Examination of the blood revealed a red-cell count of 2,330,000, with a hemoglobin of 10.5 gm. per 100 cc. and a white-cell count of 1600 with 4 per cent neutrophils, 90 per cent lymphocytes and 6 per cent monocytes. Platelets were rare in the stained film and a platelet count (Rees-Ecker method) yielded 5000 cells. The bleeding time was 71 minutes and the clotting time with standard Corning glass capillary tubes was 4 minutes. The icteric index was within normal limits. The blood Hinton reaction was negative.

The most important features of the clinical course with collateral laboratory findings are presented in Table 1. In spite of intense penicillin treatment the fever persisted, the temperature rising in step-like progression to a maximum of 105°F. on the 5th day. The cause of the fever was never clear, and except for the gingival bleeding and increasing petechial manifestations throughout the body, repeated physical examinations failed to reveal any disease. None of the agents generally used to stimulate hematopoiesis and to stop bleeding, including transfusions of folic acid, liver extracts, Lextron and intensive vitamin treatment (Cevalin and vitamin K), proved to be effective. The picture of pancytopenia persisted with slight variations and daily blood transfusions did not appear to be of any avail other than to raise transiently the level of the hemoglobin and the red-cell count. Reticulocytes could never be demonstrated. The downhill course was further complicated by a menorrhagia which started on the 1st hospital day and became increasingly more severe. Crampy abdominal pains developed, and tarry stools began to appear 1 day before death, which occurred on the 6th hospital day.

Post mortem examination revealed extensive hemorrhages both in the skin and in the internal organs, some of which appeared to be recent and some others older. All organs appeared to be affected, including the serous membranes (peri-

TABLE 1 (Continued)

DAY OF DISEASE	EOSINOPHILS	BLEEDING TIME	CLOTTING TIME	PROTHROMBIN TIME	ICTERIC INDEX	TREATMENT				
						BLOOD TRANSFUSION	CEVALIN	VITAMIN K	PENICILLIN	LEXTON
	%	min.	min.	sec.		cc.	mg.	mg.	units	capsules
1	—	71	4	55*	4	1000	200	4	1,000,000	6
2	—	—	—	—	—	1000	200	4	1,000,000	6
3	—	—	—	—	—	1000	200	4	1,000,000	6
4	1	—	—	15*	3	500	200	4	1,000,000	6
5	—	—	—	—	—	500	200	4	1,000,000	6
6	—	—	—	—	—	—	—	—	—	—

\*Control 32 seconds.

including x-ray investigation of the skull was entirely negative, electroencephalographic studies were also made and interpreted as "nonspecific." She was started on tridione treatment (0.3 gm. three times a day) and elixir of phenobarbital (4 cc. three times a day) on September 26. Examination of the blood on October 17 revealed no abnormalities. The spells became less frequent but still occasionally occurred and when the patient was seen again in early December she was advised to take Dilantin (0.1 gm.) three times a day in place of phenobarbital and to continue the tridione treatment in the amount previously prescribed. This combination proved to be effective and during the month of December the patient had only one spell. On February 18, 1947, she began to notice bleeding from the gums on brushing her teeth and the onset of fatigue. She had been warned to watch for this occurrence and therefore consulted her physician, who, in turn, referred her to a dentist. Since bleeding persisted and became more profuse, hospitalization was recommended for blood studies and treatment. All medications had been suspended when the bleeding was first reported. She entered the hospital 16 days after the onset of bleeding.

The past history was completely irrelevant except for measles as a child. In the family history the only significant data were that the paternal grandmother had died of leukemia and the paternal grandfather of anemia, the type of which was not known.

Physical examination was essentially negative, except for a maculopapular rash of the upper arms and shoulders and numerous fine petechiae over both feet. There was continuous oozing of blood from the gingival margins but the

cardium, pleura and peritoneum), the lungs, the myocardium, the mucosal lining of the large and small bowel and the internal genital organs, which appeared to be the most severely involved. The ovaries were greatly enlarged—being almost the size of a small tangerine—and were deeply infiltrated by blood. More blood was contained in the lumen of the tubes, and through the fimbrial openings about 400 cc. of blood had escaped into the abdominal cavity. Gross examination of the brain revealed a seed-sized hemorrhage in the left thalamus, and a number of punctate hemorrhages of the ring type were further found in the microscopical sections from different portions of the brain. Additional microscopical findings were large foci of extramedullary hematopoiesis in the spleen and in the mesenteric lymph nodes.

The bone marrow was examined in the sternum and in the ribs. The ribs had a dry, honey-combed appearance and were practically devoid of marrow. The sternal marrow was also scanty but showed some redness, and contained 400 red cells per cubic millimeter with 96.8 per cent blast cells, 0.8 per cent promyelocytes, 1.2 per cent myelocytes, 1.0 per cent neutrophils, 0.1 per cent eosinophils and 0.1 per cent basophils, and 1.3 per cent neutrophilic metamyelocytes, and 0.7 per cent polymorphonuclear leukocytes (Fig. 1). No erythroblasts or megakaryocytes could be seen.

### DISCUSSION

In this case, as in the similar 2 cases reported in the literature in which death followed tridione treat-



ment, a condition of aplastic anemia accounted for the fatal course of events. No other factor could be incriminated. As in the case presented by Mackay and Gottstein,<sup>6</sup> the blood condition developed several months after the patient was receiving the medication, the onset was abrupt and sudden and no available treatment could prevent the fatal outcome.

The term "aplastic anemia" carries the implication that the bone marrow has become nonfunctional. That such a concept has to be revised is, however, indicated by the well known fact that the decrease in number of erythrocytes, granulocytes and thrombocytes in the peripheral blood is not con-

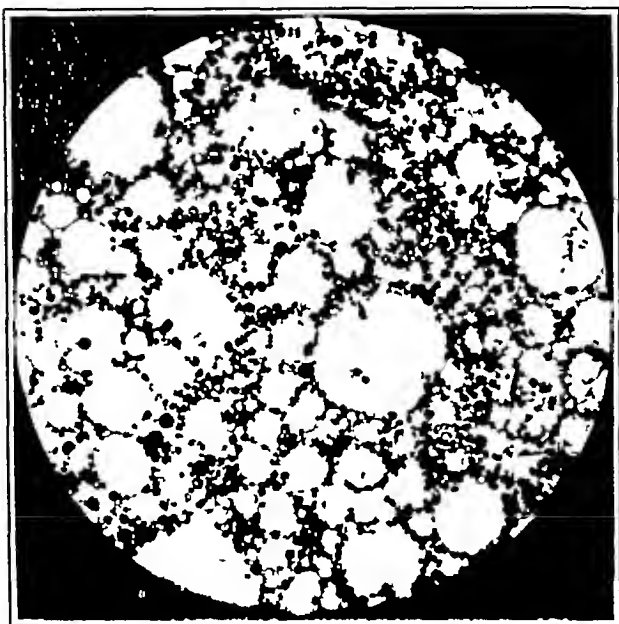


FIGURE 1 *Low-Magnification View of the Bone Marrow, Showing Active Hematopoiesis but Predominance of Lymphocytoid Cells, Interpreted as "Blast" Cells*

sistently accompanied by an aplastic bone marrow. Thompson and his associates<sup>7</sup> found marrow aplasia in only 1 of their 13 cases; there are, in addition, a number of cases on record, and certainly a larger number of unrecorded cases, in which the bone marrow appeared to be hyperplastic, with an actual increase of hematopoietic tissue, a decrease in fat spaces and a conversion of fatty marrow of the long bones into an active stage. The conception of a "maturation arrest" or of a "bone-marrow block" has been advanced to explain these cases. The classification of aplastic (refractory) anemia with hypocellular marrow, immature cellular marrow, active cellular marrow, sclerosis of the marrow and megakaryocytic marrow, proposed by Rhoads,<sup>8</sup> still stands.

Mackay and Gottstein,<sup>6</sup> in trying to analyze the toxic effect of the drug, have pointed out the structural affinity of tridione and aminopyrine, the effects

of which on the blood elements are well known. The intimate mechanism through which the drug acts on the hematopoietic system seems, however, to be various. In the case reported above, as in that of Harrison, Johnson and Ayer,<sup>5\*</sup> the drug acted upon the bone marrow, inhibiting cell maturation in all series (aplastic anemia with immature cellular marrow of Rhoads's classification). Instead, in the case of Mackay and Gottstein,<sup>6</sup> the cytotoxic effects of the drug resulted mainly in destruction of blood cells, both red and white (aplastic anemia, with hypocellular marrow, of Rhoads's classification).

In view of the bone-marrow findings and of the foci of hematopoiesis in the spleen and in the mesenteric lymph nodes the question of a possible aleukemic process (aleukemic myelosis), coincident with or precipitated by the drug treatment, arises in the case reported above. The differential diagnosis between aleukemic myelosis and aplastic anemia with hyperplastic bone marrow that in other cases might be considered a matter of academic interest becomes a matter of practical importance in the case under consideration. After thorough study of the blood smears we believe that the possibility of an aleukemic process can be ruled out, since at no time during the course of the disease were immature cells found in the peripheral blood.

With 3 fatal cases already recorded it is apparent that a good deal of precaution should be applied in the use of tridione. Mackay and Gottstein<sup>6</sup> have already stressed the point that the drug should not be administered to any patient who has had blood dyscrasia, severe anemia or hemorrhagic tendencies.

It has been advised also to use the drug in small doses at the beginning and to make frequent examinations to detect the onset of any blood disorders. In view of the possible toxic effects from the use of tridione it is essential that the drug be used only in cases for which it is particularly effective—namely, patients with petit-mal seizures. There is no sufficient evidence in the case reported above that the patient was having this particular type of seizure. The drug has already proved of such value in the control of convulsive disorders that the few fatal cases resulting from its use should not discourage its further administration. Certainly, one might feel safer in prescribing the drug if a new chemical product could be found of equal therapeutic efficacy but deprived of toxic effects, or if some methods could be developed to measure the concentration of the drug in the blood during the treatment and the sensitivity of the patient to the drug itself before the treatment is started.

#### SUMMARY

A fatal case of acute pancytopenia following the use of tridione is reported, with a brief review of 2

\*It is possible that the bone marrow cells that we considered as blast cells corresponded to the cells interpreted by Harrison, Johnson and Ayer as lymphocytes (lymphoidocytes of Pappenheim and Maximow).

other fatal cases so far recorded. A note of caution is sounded regarding the administration of this drug and its potential danger, as well as the necessity of frequent blood examinations. A plea is made to limit the use of tridione to the control of true petit-mal seizures.

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## NEUROLOGIC COMPLICATIONS OF TRICHINOSIS\*

## Report of Two Cases

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ALTHOUGH increasing attention has been paid to trichinosis in recent years, relatively little has been reported concerning its neurologic complications. Drowsiness, headache, depression and delirium are observed to be common findings. Frank meningeal irritation, hemiplegia, aphasia and other localized neurologic manifestations occur in from 10 to 17 per cent of all cases,<sup>1, 2</sup> but there are often no changes in the cerebrospinal fluid. The manner in which the infestation affects the brain has never been clearly demonstrated, although it is assumed that small cerebral vessels are occluded by the parasite. The prognosis of the cerebral symptoms in this disease is correspondingly uncertain. Indeed, it appears possible for neurologic manifestations to occur with few other clinical signs of the disease.

The following cases illustrate some of the difficulties encountered in diagnosis.

**CASE 1.** S. T., a 60-year-old Polish born woman was admitted to the hospital on October 29, 1946. She had been well until about 2½ weeks before admission when mild nausea and pain in the lower abdomen developed. Two weeks before admission she and her family noted the onset of periorbital edema with retrobulbar pain. This was not accompanied by fever, rash or local inflammation. The periorbital edema increased rapidly for 2 or 3 days, until both eyes were swollen shut. Ten days before admission generalized myalgia, particularly in the legs and anorexia developed. The swelling of the eyelids disappeared after 5 days, but 2 days later the temperature rose to 104°F. and chills, nausea and vomiting occurred. Despite the administration of sulfonamides by a physician the patient became progressively weaker and anorexic.

One week before admission she first became incontinent, appearing to show no concern over wetting or soiling the bed. She developed increasing apathy, and although she continued to recognize her family and friends, she became increasingly confused and was stated to have thrown her arms about in purposeless movements.

A further history obtained from the patient and from her relatives revealed the fact that she had obtained a portion of a pig from friends, about 4 or 5 weeks before admission and had eaten a rather large amount of the meat. Her family refused to touch the pork which had tasted spoiled to them. The friend who owned the animal was said to have suffered from periorbital edema and nausea several days before the onset of the patient's illness.

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Physical examination revealed an obese woman apparently aware of her surroundings but rather apathetic. The skin showed the changes produced by mild dehydration. There was no lymphadenopathy. No muscular soreness could be elicited. The lungs were clear to percussion and auscultation. The heart was not enlarged. There was a Grade I diastolic murmur at the apex. The liver was palpated one fingerbreadth below the costal margin.

The pulse was 112, and the blood pressure 120/82.

Neurological examination showed the following abnormalities. The patient lay quietly in bed with her eyes closed. Occasionally but not consistently she responded to simple commands if they were repeated several times (whether in English or Polish seemed unimportant). Any movement was soon discontinued as though in weariness or apathy. Orientation in time and space was apparently excellent and although she did not initiate conversation either with the examiner or with her family, on further examination this fact was deemed to be more the result of drowsiness and apathy than true aphasia.

The left arm and left leg were considered to be slightly flaccid as compared with the right arm and right leg, but all reflexes were found to be normal at that time. There was some slight nuchal rigidity.

Examination of the urine showed 20 to 30 white cells per high power field. Examination of the blood disclosed a red cell count of 4,380,000 and a white-cell count of 12,250 with 53 per cent neutrophils, 38 per cent lymphocytes and 5 per cent eosinophils. Lumbar puncture demonstrated an initial spinal fluid pressure equivalent to 110 mm. of water and xanthochromic fluid containing 700 crenated red cells per cubic millimeter with a total protein of 11 mg. and a sugar of 85 mg., and a chloride of 708 mg. per 100 cc. Three days later a second lumbar puncture again showed a yellow fluid with a pressure equivalent to 140 mm. of water that contained 540 fresh red cells per cubic millimeter with a total protein of 11 mg. per 100 cc. and a gold sol curve of 0001110000. The spinal fluid Hinton and Wassermann reactions were negative. An electrocardiogram revealed myocardial disease, the T waves being inverted in Lead I, diphasic in Leads 2 and 4, and of low voltage in Lead 3.

Six days after admission, the reflexes in the right arm and right leg were found to be slightly more active than those on the left and the right plantar response was equivocal. Two days later the right plantar response was definitely extensor. A Trichinella antigen skin test on the 7th hospital day was equivocal but when repeated on the 8th day it was definitely positive. The patient at that time was thought to be of normal mental status. On the 22nd hospital day the daily differential blood smears showed a rise in the eosinophil count to 13 per cent and thereafter during the patient's stay remained at about this level with a continuing relative lymphocytosis. A number of examiners agreed that the muscles were neither indurated nor tender. Nevertheless a small muscle biopsy from the left medial gastrocnemius was taken on the 8th hospital day and upon section showed several fine examples of freshly encysted trichinae. The continued tachycardia

caused some concern, and mobilization was made extremely gradually. Late in the convalescence pain developed upon deep breathing just over the two lower ribs on the left. X-ray study showed some consolidation in that area, and the patient was treated successfully with penicillin and discharged. She continued to improve rapidly, although on discharge 5 weeks after admission she still had an extensor plantar response and increased deep tendon reflexes on the right.

**CASE 2** W K, a 40-year-old toolmaker, was admitted to the hospital on October 31, 1944. He had been well until 3 weeks before admission, when he noticed the onset of "sick feelings," nausea, chilly sensations, a temperature of 101°F and a slight nonproductive cough. Within a day, increased nausea and vomiting developed, and he continued to vomit intermittently. During the same period he also experienced abdominal discomfort, diarrhea and mild pains in the muscles, including the wrists, arms, legs and back. The exact order of the appearance of these symptoms was not clear. The symptoms progressed until 5 days before admission, when they became so severe that he was forced to leave his work and spend the day in bed. It was then that he first noted "spots before the eyes," conjunctivitis, increased lacrimation and periorbital edema. He drank some tea and whisky and remained in bed until the night before admission, when his family physician recommended hospitalization.

The diagnosis of trichinosis was immediately suspected, and on questioning the patient stated that the only pork that he had consumed recently had been obtained at a restaurant a few days before the onset of the symptoms and that several other men who had eaten at the same restaurant had identical, although less severe, symptoms.

The past, family and social histories were not contributory.

Physical examination was entirely negative except for conjunctivitis, periorbital edema and a blood pressure of 100/70. Neurologic examination was negative, although the patient was noted to be restless and apprehensive about his condition.

Examinations of the blood showed a white-cell count ranging between 11,000 and 14,500, with 44 per cent eosinophils, which gradually increased to 64 per cent during the 3 weeks that the patient remained on the ward. The urine was normal. Lumbar punctures on the 19th and 24th hospital days were normal in all respects. Electrocardiographic tracings taken 2 and 8 days after admission showed sinoauricular tachycardia, low voltage and low origin of the ST segments in all leads. These were interpreted as showing myocardial damage.

On the 4th day the patient showed increased restlessness, and his movements were said to be jerky. He demonstrated great apprehension and anxiety, and in view of these complaints he was given paraldehyde. Despite medication he became increasingly restless, noisy and disoriented, and it was necessary to place him in restraint. He showed no tremor of the hands or tongue suggestive of delirium tremens. Infusions were given, and during the night 0.25 gm of luminal sodium was required to quiet the patient. The next morning the blood pressure was unobtainable and the patient's condition was critical. He then began steadily to improve. After the next 4 or 5 days it was noticed that the patient had difficulty in walking, and neurologic examination on the 20th hospital day demonstrated a slight left hemiparesis. There was an extensor plantar response on the left and a positive Hoffmann reflex in the left hand, together with slightly more active knee and ankle jerks in the left leg. The patient was noted to drag the left leg in walking, and when it was extended and elevated it "drifted" downward in marked contrast to the right leg. Position sense was also found to be impaired in the fingers and toes on the left. On the 25th hospital day the reflexes were slightly more active on the left than on the right, and an extensor plantar response was still present on the left side.

During the following 4 days, until discharge 1 month after admission, he showed gradual improvement in his ability to walk. His apprehension and anxiety disappeared completely.

Five months later the patient was readmitted to the hospital for incipient delirium tremens, and at that time it was noted that the gait was unsteady, difficulty apparently being limited to the left leg. Vibration and position senses were impaired in the left leg, with hypesthesia, and there was an extensor plantar response in the left foot.

Unfortunately, no muscle biopsy was taken on either of the admissions, and the diagnosis of trichinosis must therefore remain presumptive, although there seems little reason to doubt the nature of the disease in the presence of such a characteristic history and with the progressive increase in the eosinophilic differential count.

## DISCUSSION

Since an adequate review of the literature pertaining to the manifestations of infection by *Trichinella spiralis* may be found in Gould's<sup>1</sup> excellent monograph, no extensive recapitulation need be attempted in this report. The cerebral lesions were described by Most and Abeles,<sup>3</sup> who found three types of microscopic changes in the brain at autopsy: the presence of granulomatous nodules, described as being a dense collection of cells occurring most frequently throughout the subcortical white substance and consisting of lymphocytes, plasma cells and a third large cell with a vesicular, polymorphous nucleus, with another type of nodule consisting mainly of microglial elements, the appearance of the parasite in the parenchyma of the brain, the parasites being the filariform larvae and being found in the nodules described above, the evidence of pathologic alterations in and around the blood vessels—there was extensive perivascular infiltration with fibroblasts, plasma cells, polymorphonuclear cells, gutter cells and small darkly staining cells resembling lymphocytes. The authors also remarked upon the numerous small hemorrhages in the periventricular areas below the ependymal layer. No large hemorrhages were noted.

The disordered mental state and the residual neurologic signs were the remarkable features of the 2 cases reported above. In Case 1 the mental status was remarkable for the severe depression, which, upon gradually clearing, disclosed a deep lethargy that persisted for some days longer. In Case 2, the picture was one of an acute delirium so similar to that encountered in acute and chronic alcoholism that the patient was thought for a time to be suffering from delirium tremens. It is also interesting that the delirium occurred three weeks after the onset of symptoms and lasted only two days, although the patient was said to have been restless and apprehensive during the earlier weeks. In the first case reported by Most and Abeles<sup>3</sup> the patient was described as being severely depressed, with clouded mentality and some evidence of mild disorientation. Their second patient was also disoriented and to a greater extent, with severe difficulty in recent and remote memory. The lethargy and depression are particularly interesting as special manifestations of only a limited number of diseases and are not so nonspecific as simple delirium. In the large number of cases reported by Sheldon<sup>2</sup> in the Wolverhampton epidemic, depression and lethargy were common to almost all patients. It is extremely difficult to decide whether this peculiar mental state results from damage to the nervous system or

whether it is only a concomitant effect of severe illness. It is of some significance, however, that these symptoms have seldom been noted in cases that presented no focal neurologic signs. That this is not simply a measure of the severity of the general infection is indicated by the cases reported by Spink,<sup>4</sup> in many of which the infection was fatal without neurologic involvement. It therefore seems reasonable to postulate diffuse damage to the brain in at least some cases since the pathological material in the cases of Most and Abeles<sup>2</sup> demonstrated widespread affection of nervous tissues. In the case reported by Stern and Dancy,<sup>5</sup> the patient had shown severe psychotic tendencies before the onset of trichinosis, and it seems most reasonable to assume that the major psychosis that appeared with the height of the infection was only the result of a severe sickness.

The signs of focal damage to the nervous system gave certain evidence of central-nervous damage in the cases reported above. In Case 1 there was a mild hemiplegia on the right with an extensor plantar response on the same side that could still be elicited upon discharge five weeks after admission. The patient in Case 2 showed a left hemiplegia with loss of position and vibration sense in the extremities, together with an extensor plantar response. On readmission five months later some ataxia, with loss of position and vibration senses, and the extensor plantar response were still present. The lesion in the right cerebral cortex was thus of a destructive nature rather than a transitory vascular or toxic change. In Spink's<sup>4</sup> fourth case, a right hemiplegia was present together with aphasia, and these symptoms were of sudden onset. It seems necessary to postulate a sudden vascular occlusion to account for such signs. One of the cases of Most and Abeles had shown a hemiplegia, and the other showed absent deep tendon reflexes in the lower extremities with absent biceps reflex in the upper extremities. No vascular occlusion was found, but there was abundant evidence of perivascular infiltration, generalized engorgement and hyperemia. Absence or decrease of the tendon reflexes is a common neurologic finding in cases of trichinosis, as in Merritt and Rosenbaum's<sup>6</sup> second case, and probably indicates damage to the spinal cord. Sheldon<sup>7</sup> estimates that 17 per cent of all cases seen in the epidemic in Wolverhampton gave evidence of focal neurologic damage. Some of his patients showed cerebellar signs, and indeed in several cases dizziness, cerebellar ataxia and nystagmus were the presenting symptoms and signs before any evidence of general trichinosis appeared.

Case 1 presented three unusual features. In the first place, repeated eosinophilic counts during the

entire period of observation failed to reach the high level commonly reported. In addition the count was slow in rising, in spite of proved heavy infestation. Gould<sup>1</sup> remarks that this is a poor prognostic sign. Secondly, although no muscular tenderness or induration could be established, even though it was especially sought, a biopsy taken from the muscle most readily accessible — the gastrocnemius — demonstrated without difficulty the presence of the parasite. This finding indicates that the absence of persisting induration and tenderness does not exclude infection. Thirdly, on two successive occasions lumbar punctures disclosed spinal fluid containing 500 to 700 red cells per cubic millimeter and showing xanthochromia. It did not appear possible for the blood to have been introduced by the lumbar-puncture procedure. From the findings of Most and Abeles it appears that multiple periventricular hemorrhages had occurred.

In view of the high liability to epilepsy resulting from other parasitic infection of the brain, particularly from cysticercosis, it is remarkable how seldom this complication is reported after trichinosis. Dandy<sup>7</sup> has reported a case followed by grand-mal seizures ten years later. The cerebral lesions in cysticercosis, however, are reported to be more superficial than those of trichinosis, and the lessened liability may arise from this difference. There is much need for further pathological study and above all for wider recognition of the fact that neurologic signs and symptoms of a protean type are a frequent result of *Trichinella* infestation.

### CONCLUSIONS

The cases presenting cerebral involvement in trichinosis reported above indicate that the disease must be suspected in unexplained apathy and stupor with transient signs of damage to the central nervous system. The characteristic history of ingestion of suspected pork followed by periorbital edema, diarrhea with muscular pains and tenderness is occasionally lacking. Absence of persisting muscular tenderness and induration does not negate heavy muscular infestation, and the eosinophilic count may not be greatly changed.

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## ACANTHOSIS NIGRICANS\*

## Report of a Case Associated with Thyroid Cancer

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**A**CANTHOSIS nigricans associated with cancer of the thyroid gland has apparently never been recorded in human beings. The following case is therefore of particular interest.

A 33-year-old Negress was admitted to the Surgical Service of the University of Virginia Hospital on February 1, 1947, complaining of shortness of breath of 1 month's duration.

In December, 1944, the patient had had a rapid onset of tremulousness, palpitation, dysphagia, exertional dyspnea, progressive weight loss and painless tumor formation in the anterior portion of the neck. On February 26, 1945, she had been admitted to another hospital, where the thyroid gland was found to be enlarged, and the basal metabolic rate in-

gressive dysphagia, dysphonia, exertional dyspnea, anorexia and weakness. On admission she was able to swallow only fluids.

The patient had always been obese. Facial hirsutism and hyperpigmentation had been present since girlhood. An appendectomy had been performed in 1936. Routine blood serologic tests for syphilis were repeatedly positive in May, 1942, when a diagnosis of late latent syphilis was made. Subsequently the patient received inadequate treatment with arsenicals and bismuth. The menstrual history was normal.

Hirsutism and obesity were prominent among female relatives on the maternal side of the family. The patient's 5-year-old daughter had intense facial hirsutism. There was no family history of cancer and no past or family history of cutaneous disease.

The patient was extremely obese, weighing 289.5 pounds (131.5 kg). There were numerous long, silky, lanugo hairs on the upper lip and on both sides of the face. At the base of the nose there were two smooth, oval, hyperpigmented, macular patches extending over to the adjacent infraorbital regions, each measuring 4 cm in diameter. A striking pigmentary eruption was distributed in the natural folds of the skin of the neck, axillas, inframammary and inguinal regions, cubital and popliteal spaces and gluteal cleft, with velvety, hyperpigmented papules and verrucous lesions aggregated into patches arranged parallel to the long axis of the skin folds (Fig 1). There were large, thick hyperkeratoses on the soles. The mucous membranes, fingernails and toenails were normal. A large, fixed, smooth, nontender, indurated mass occupied the whole anterior portion of the neck in the submental and thyroid regions. The mass effectively limited motion of the head and neck. There was a well healed thyroidectomy scar. Movement of the right side of the thorax was limited, with impaired resonance and diminished to absent breath sounds over the entire right lung. Examination of the abdomen was not satisfactory because of extreme obesity, an operative scar of the right rectus muscle was present. No abdominal masses were felt. The liver and spleen were not palpable. There was slight pitting edema over both tibias.

The temperature and pulse were normal, and the respirations were rapid and labored. The blood pressure was 150/80.

Routine laboratory studies showed nothing remarkable. The blood Wassermann and Kahn reactions were repeatedly positive. Owing to the patient's poor general condition, a lumbar puncture was not performed. A Robinson-Power-Kepner<sup>1</sup> test for adrenal cortical insufficiency was within the limits of normal — although the total volume of urine voided during the night was greater than any one of the hourly specimens obtained during the morning, procedure 2 of the test gave a value of 73.5, which is considered normal.

A roentgenogram of the chest showed massive effusion in the right pleural cavity, with swelling of the soft tissues posterior to the trachea opposite the seventh cervical and first thoracic vertebrae. After the withdrawal of 2400 cc of sanguineous fluid, repeated roentgenograms of the lungs demonstrated an area of lobulated, homogeneous density extending throughout the posterior portion of the right lower lung field. This was considered to represent metastatic tumor.

The patient had decided respiratory discomfort throughout her stay in the hospital. She was relieved by six thoracenteses in the first 10 days, with withdrawal of a total of 4460 cc of sanguineous fluid from the right pleural cavity. Examination of a centrifuged specimen of this fluid disclosed no tumor cells. Laryngoscopic examination showed extension of the tumor tissue into the left ventricular fold, with resultant fixation of the left true and false vocal cords. The right side was not involved.

Histologic examination of a specimen of skin from the posterior cervical region revealed the characteristics of



FIGURE 1 Cutaneous Lesions of Acanthosis Nigricans, Showing Hyperpigmentation and Verrucous Changes

creased. A diagnosis of hyperthyroidism was made, and a subtotal thyroidectomy performed. A large colloid cyst was found occupying the left lobe of the thyroid gland. There were several smaller, similar cysts in the right lobe. Four fifths of the left lobe and three fourths of the right were removed. Microscopical study of the tissue disclosed the presence of cancer. Postoperative roentgen-ray therapy consisted of 2400 r to the thyroid region, divided into fifteen treatments. In January, 1946, a little over 1 year after the onset of the illness, the patient noticed small, rough, dark, warty, symptomless papules in the axillas. She paid little attention to these lesions, which increased only slightly in size and number. At no time was she aware of similar lesions elsewhere on the body. After the last x-ray treatment in September, 1946, she was asymptomatic until January, 1947, when the mass in the neck returned and she developed pro-

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acanthosis nigricans (Fig 2 and 3). There was distinct papillomatosis of the cutaneous surface with decided hyperkeratosis. An irregular acanthosis with many finger-like rete ridges was present, although most of the prickle-cell layer was relatively thin and atrophic. The depressions between the epidermal projections were filled with keratin. There was dense melanin pigmentation of the basal cells. The long, narrow papillary bodies contained moderate numbers of pigment-laden chromatophores. The cutis showed no abnormal changes.

Histologic examination of tissue obtained from the thyroid gland showed a malignant tumor composed of broad sheets of spindle-shaped cells containing large vesicular nuclei. These cells varied somewhat in size and form with no particular pattern of growth. Numerous mitotic figures were present. There were many large blood spaces in which the tumor tissue was in direct contact with the blood stream. No recognizable thyroid tissue was seen. On the basis of cell type, this tumor was considered to be mesoblastic in origin. The histologic diagnosis was anaplastic malignant tumor probably of mesoblastic origin.

The patient was given deep filtered roentgen ray therapy in divided doses for a total of 4050 r to the anterior and posterior aspects of the right side of the thorax. Treatment resulted in moderate relief of malaise and respiratory difficulty.

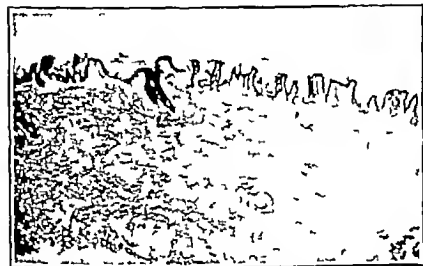


FIGURE 2. Photomicrograph of Skin from the Posterior Cervical Region Showing the Characteristic Structure in Acanthosis Nigricans

Because of previous treatment no x ray therapy was given to the mass in the neck.

During hospitalization the cutaneous eruption showed increase in pigmentation. The patient was instructed to return in 1 month after discharge from the hospital. It was later learned from her physician that she had died suddenly at home of a pulmonary hemorrhage 47 days after discharge.

#### DISCUSSION

Curth's<sup>2</sup> recent review has contributed greatly to a better understanding of the nature of this unusual pigmentary disorder of the skin.

Acanthosis nigricans may be confused clinically with Addison's disease, hemochromatosis and arsenical pigmentation. The clinical and histologic features of these diseases have been described in detail by Montgomery and O'Leary.<sup>3</sup>

The cause of acanthosis nigricans remains unknown. The disorder has been reported in association with a number of conditions, affecting directly or indirectly the chromaffin and sympathetic systems. Among the conditions supposedly related to the cause are metabolic disturbances, toxins, endocrine diseases, tuberculosis, syphilis, congenital

abnormalities, hereditary factors and inflammatory and traumatic lesions of the stomach and chromaffin systems. Curth's<sup>2,4</sup> studies suggest a genetic relation between acanthosis nigricans and certain types



FIGURE 3. Enlargement of a Portion of the Section Shown in Figure 2. The hyperkeratosis, acanthosis and pigmentation are striking.

of cancer, and a common origin for both the benign and the malignant forms of the disease.

The site of the associated primary cancer is almost invariably in the abdomen. Curth<sup>2</sup> found 92.6 per cent originating in the abdomen, the majority of which were located in the gastrointestinal tract. Other reported cases arose from the uterus, chorion and liver.

In some cases the primary site could not be determined. Questionable renal, esophageal and pancreatic carcinomas have been reported. In some cases of acanthosis nigricans the primary tumor was found in the mediastinum, lung and breast. A case in a dog with medullary carcinoma of the thyroid gland, with metastasis to the lung, liver, kidney and lymph nodes, was reported by Schindelfer.<sup>5</sup>

Curth believes that disturbances of the thyroid gland are frequently seen with acanthosis nigricans. Masson and Montgomery's<sup>6</sup> and Curth's patients had thyroid adenomas. These findings may be coincidental.

It is believed the patient in the case reported above had a primary malignant tumor of the thyroid gland. The onset of the disease and the clinical course suggested an origin in the thyroid gland, with metastasis to the lung. Unfortunately, an autopsy was not performed.

Malignant mesoblastic tumors of the thyroid gland appear to be infrequent. Many tumors described as sarcomas are evidently highly anaplastic carcinomas. Ewing<sup>7</sup> regards the mesoblastic origin of most of the sarcomas reported in the literature as highly improbable, and believes that the occurrence of true thyroid sarcoma in man still requires demonstration.

There is a widespread belief that adrenal disease or dysfunction participates in the production of pigmentary changes in acanthosis nigricans. Curth,<sup>2</sup> in a comprehensive review, has considered the existing evidence, which consists of post-mortem findings of involvement of the adrenal gland by metastatic cancer in cases of the so-called "malignant type." Metastases to the adrenal glands are apparently of no etiologic significance, since they occur in only a small number of these cases, and not at all in those unassociated with cancer.

In the case reported above, the presence of a latent syphilitic infection was not considered significant. The patient's obesity and hirsutism were evidently of familial origin, although an endocrine cause could not be excluded without post-mortem examination.

In this patient, as in 2 other cases reported from this clinic,<sup>8,9</sup> there was no evidence of adrenal cortical insufficiency as measured by a test of urinary sodium chloride excretion.

The cutaneous eruption and the malignant tumor are usually discovered at the same time, but the

skin changes may precede or follow detection of the cancer.<sup>2</sup> Since the cutaneous alterations are more easily perceptible than the tumor, their earlier recognition may be only apparent.

Exceptionally, as in the case reported above, the eruption follows the appearance of cancer. The explanation may lie in accessibility of the tumor for diagnosis or in poor observation on the part of the patient.

#### SUMMARY

A case of acanthosis nigricans occurring in association with a malignant tumor, probably carcinoma, of the thyroid gland in a thirty-three-year-old Negress is reported.

The literature regarding this unusual pigmentary disorder of the skin is briefly discussed.

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## MORPHINE HYPERSENSITIVITY IN KYPHOSCOLIOSIS\*

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THE benefits derived from the therapeutic use of morphine in a wide variety of clinical disorders are well appreciated and properly exploited by physicians. At the same time it is recognized that a small but important group of diseases may be aggravated by morphine. This phenomenon may be entirely separate from any individual allergic reaction and applies, potentially, to all persons suffering from such diseases. Mechanical obstruction in the bronchial tree, bronchial asthma and myxedema represent common examples of diseases falling within this category in which the use of morphine is contraindicated.

Much less well known as a serious contraindication to the use of morphine is heart failure asso-

ciated with, or due to, kyphoscoliosis. Two recently encountered cases (1 fatal) of such a reaction to ordinary therapeutic dosage are reported.

#### CASE REPORTS

**CASE 1** J. R., a 49-year-old hotel watchman, re-entered the Boston City Hospital in May, 1946, with the complaint of swelling of the legs.

At the age of 7 years a heavy iron gate had fallen on the patient, fracturing the spine and causing paralysis of the lower half of the body. He required hospitalization for a prolonged period and later wore a back brace for 7 years. As a result of the accident he had a marked "hunch-back" deformity. The patient subsequently enjoyed excellent health until his 48th year, when he began to experience dyspnea on ordinary exertion. In April, 1945, he developed a respiratory infection and was admitted for the first time to the Boston City Hospital. At that time he was found to have kyphoscoliotic heart disease, with pulmonary edema and lobar pneumonia. X-ray study of the chest showed consolidation of the right lung due to pneumonia, and marked kyphoscoliosis. The vital capacity was 700 cc. and 500 cc. on two examinations. Treated with penicillin, later supplemented by digitals and mercurial diuretics, the patient made slow but ultimately satisfactory progress, and was discharged after 6 weeks' hospitalization. In March, 1946, dyspnea returned and was soon followed by the development

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of massive edema of the legs and enlargement of the abdomen Two days prior to re-entry urinary retention developed

Physical examination revealed a poorly nourished deformed man who was orthopneic and coughing frequently. The lips were cyanotic. There was marked thoracic kyphosis and scoliosis to the right, associated with a pigeon-breast deformity of the chest. Numerous rales were heard throughout both lung fields. The heart borders could not be satisfactorily outlined by percussion. The cardiac rate was 125, the heart sounds were of good quality with accentuation of the pulmonary second sound. There were no thrills or murmurs. The abdomen was distended and there was tenderness over the liver shifting dullness was elicited. The urinary bladder was palpated almost to the level of the umbilicus. The prostate gland was enlarged. Edema of the legs was marked. The fingers showed slight clubbing.

The respirations were 30 per minute. The blood pressure was 120/90 in both arms.

Very little benefit resulted from the use of oxygen, digitalis, theophylline and mercurial diuretics. Cyanosis, orthopnea and cough persisted. The patient was very restless and being unable to void, required catheterization frequently. At 7:15 p.m. on the 6th hospital day 10 mg. of morphine sulfate was given subcutaneously in preparation for catheterization. This was the first time the drug was used. In 15 minutes the respirations diminished to 2 per minute. Continued use of oxygen and frequent administration of caffeine and Coramine temporarily increased the respirations to 10, but the patient became comatose. At 8:00 a.m. on the 7th hospital day the respirations were deep and irregular, the rate being 4 per minute. The blood pressure fell to 70/0. The pulse became increasingly rapid and thready. At noon the patient expired.

CASE 2. N.F. a 65-year-old housewife entered the Boston City Hospital on September 6, 1946 with the complaint of shortness of breath and swelling of the legs.

The patient had apparently been in good health until 6 months previously, when she began to note dyspnea on exertion. This progressed in severity until it interfered with her usual household activities. About 1 month prior to admission edema of the legs had developed and further interfered with her activities, the patient being finally restricted to bed and a chair. Shortly before admission she began to cough because of this and the dyspnea she was unable to sleep at night. There was no history of symptoms referable to the gastrointestinal or genitourinary system.

Physical examination revealed an obese woman sitting up in bed who was orthopneic and apparently acutely ill. The skin and mucosae were slightly cyanotic. The retinal vessels showed increased tortuosity and arteriovenous nicking. The neck veins were distended. There was moderate dullness over both lung bases with numerous medium rales audible during inspiration over the lower halves of both lungs. The heart was moderately enlarged to percussion, the border of cardiac dullness extending to both the left and the right. The cardiac rate was 98 per minute, with a regular rhythm. The heart sounds were of good quality with accentuation of the pulmonary second sound. Loud systolic murmurs were heard over the mitral valve and aortic valve areas. There was no thrill or friction rub. The abdomen was obese and slightly distended. The liver and spleen could not be felt. Both legs showed marked pitting edema with superficial maceration of the skin. The vital capacity was 1100 cc. A x-ray study of the chest revealed thoracic scoliosis to the right side, cardiac enlargement and pulmonary congestion.

The respirations were 26 per minute. The blood pressure was 260/110 in both arms.

The patient was digitalized within 24 hours, and initially showed diminution in the pulmonary congestion. However, at midnight of the 3rd hospital day she became more acutely ill manifesting severe dyspnea, cough and increased cyanosis. Oxygen was administered, and theophylline given intravenously. At that time 10 mg. of morphine sulfate was also given subcutaneously. An hour later the patient was found to be comatose. Respirations were deep and regular, the rate being 5 per minute. On further administration of oxygen and with frequently repeated doses of caffeine and Coramine there was slow but gradual improvement in the respiratory rate and general condition. Twenty-four hours later the patient was alert and essentially symptom free. On the 6th hospital day a test dose of 4 mg. of morphine sulfate was given subcutaneously. Over a period of 2 hours the

respirations declined from 26 to 16 per minute and became Cheyne-Stokes in character. Morphine was not administered again.

## Discussion

Two recently published reports have directed attention to the untoward effects of narcotic drugs in depressing the respirations of patients with kyphoscoliosis. In the course of a study of the decrease in functional capacity of the lungs and heart resulting from deformities of the chest, Chapman, Dill and Graybiel<sup>1</sup> observed two critical reactions—one resulting from Pantopon, and the other from morphine. Daley reported 3 patients whose deaths while in cardiac failure were precipitated by the administration of morphine. In 2 cases fatal respiratory depression occurred one hour after the use of morphine in a dosage of 15 mg. In the third case, only 5 mg. was used, but this patient—who suffered, in addition, from diffuse bronchial infection—died seventy-five minutes later with signs of acute respiratory depression.

It has been shown that persons with kyphoscoliosis may suffer from a combination of handicaps, all of which contribute to produce increasing anoxia. The skeletal deformity limits the motion of the ribs and leads to inefficient action of the intercostal muscles and the diaphragm.<sup>2</sup> Compression of the lung on the concave side of the deformity and emphysema on the convex side further reduce the vital capacity, and at the same time diminish the total effective surface for transalveolar gaseous exchange. The result of these skeletal, muscular and pulmonary abnormalities is diminished oxygen saturation of the arterial blood. With the additional handicaps of cardiac failure, respiratory infection or diminished oxygen content in the inspired air (as with inhalational anesthesia or exposure to high altitudes) respiratory embarrassment may become extreme.

The effect of morphine in such situations, apparently, is occasionally disastrous. As in the 2 cases reported above and the others referred to, asphyxia of the patient occurs from one or more of the following effects: a central depressant action on respiration, a depression of cough reflex, a tendency to accentuate bronchial spasm through its cholinergic action and a general hypnotic and pain-relieving action resulting in generally diminished muscular tone.

In normal subjects the administration of carbon dioxide stimulates both the depth and the rate of respiration. After morphine the inhalation of carbon dioxide stimulates the depth rather than the rate.<sup>3</sup> In kyphoscoliosis complicated by some additional condition interfering with pulmonary ventilation, if the depth of respiration is already maximal and fixed, the effect of a lowered respiratory rate induced by morphine can only be one of increased anoxia. The work of Peterson, Bornstein and Jasper<sup>4</sup> indicates that when there is a diminution of the oxygen



available to the pulmonary capillary blood, any drug that blocks pain sensitivity or induces bodily relaxation and general loss of tone results in shallow breathing, with lower oxygen saturation of the arterial blood

We do not believe that the exaggerated effect from morphine is in any way specific for patients with kyphoscoliosis. Our experience suggests that any patient suffering from long-standing lung disease with pulmonary decompensation complicated by heart failure presents similar predisposing handicaps, which might make the added effects of morphine lethal. A sampling of recent case records at the Boston City Hospital of patients suffering from chronic cor pulmonale without kyphoscoliosis lends further support to the impression that these patients are often adversely affected by morphine. These records show numerous cases of severe respiratory depression following the use of such medication in therapeutic dosage. Spain and Handler<sup>6</sup> indicate that they became aware of this hazard during their review of 60 cases of cor pulmonale, and they warn

against the use of narcotic drugs in patients suffering from this disease

### SUMMARY

Two cases exemplifying the adverse effect of morphine on kyphoscoliotic patients with pulmonary cardiac failure are presented. The major physiologic and pathologic factors in the causation of this sensitivity are discussed. It appears probable that persons with decompensated cor pulmonale, but without kyphoscoliosis, will show a similar sensitivity.

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## MEDICAL PROGRESS

### ABDOMINAL SURGERY

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**D**URING the past year, the literature regarding surgery involving the abdominal region has been voluminous. Many studies pertaining to important variations in anatomic arrangements have been made. Lesions related to congenital defects and their effect on surgical conditions within the abdomen are significant. Detailed follow-up reports concerning life expectancy, especially in patients with malignant tumors, are helpful. Comparative results of the surgical treatment of common disorders in successive years, showing the marked improvement in morbidity and mortality, are impressive. Only articles giving new technics or approaches to usual conditions and those relating to rare disorders can be stressed in this report for lack of space. Some interesting reports are not mentioned either because the subject has been discussed in recent progress reports or for reasons given above. Tribute is due the numerous authors who are contributing to the advance of surgery through their publications.

#### THE ABDOMINAL WALL

Singleton,<sup>1</sup> who was one of the rare surgeons of our time interested in teaching applied anatomy, has left behind a fine contribution on abdominal in-

cisions. He has long championed anatomic approaches to the abdominal viscera and firmly believed that the average surgeon gave this important subject too little thought. His last article is well illustrated and will be a helpful reference. He advocates long, oblique incisions extending well into the flanks, which allow the lateral muscles to be separated in the direction of their fibers while the strong rectus muscle is freed from its fascia and retracted without transection. Excellent exposure to the more remote areas of the abdomen can thus be obtained with little risk of dehiscence or post-operative hernia. The extra time involved in making these approaches and closing the defects seems warranted on the basis of his comparative studies.

Gurd<sup>2</sup> gives a good description of the transverse abdominal incision. He believes that most surgeons do not understand the principles of such approaches and considers transection of the rectus muscles, either 2.5 cm above or 2.5 cm below the umbilicus, to be correct. Attention is called to the importance of separating the lateral muscles of the abdominal wall in the direction of their fibers. Care that the nerve supply be visualized and that not more than one of the lateral nerves be severed is stressed.

Wiley and Sugarbaker<sup>3</sup> have made a comparative study of the use of steel-wire, catgut and silk-layer

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closure in a small group of cases. Steel wire was most satisfactory, since it was associated with fewer cases of wound dehiscence, infection and post-operative hernia. Many of the patients were elderly and were operated upon for malignant tumors. Stay sutures were used in only 35 per cent of the wounds closed by the catgut and silk technics.

### HERNIA

Follow-up results on 1039 of 1545 cases of hernia repair at the New York Hospital have been reported by Glenn.<sup>4</sup> The incidence of recurrences was as follows: indirect inguinal, 3 per cent; direct inguinal, 8.1 per cent; recurrent inguinal, 14.7 per cent; femoral, 8.5 per cent; umbilical, 11.8 per cent; epigastric, 9 per cent; and postoperative ventral, 12 per cent. Fine silk sutures were generally used. The cord was transplanted in 188 and not transplanted in 610 cases. There were 3 deaths in the series. Glenn believes that fascial repair would not have given better results but apparently bases this opinion on the experience of others.

Garner<sup>5</sup> analyzes the results of 2643 hernia repairs. In primary cases, catgut to Poupart's ligament gave 10 per cent recurrences and silk 7 per cent, whereas silk to Cooper's ligament resulted in only 3.4 per cent recurrences. In recurrent cases the use of Cooper's ligament gave poorer results with silk repair than those in which Poupart's ligament alone was used. The results with Galie repairs were better than those with McArthur's technic.

Gaston<sup>6</sup> and Christopher and Penna<sup>7</sup> have had favorable results with the McArthur fascial repair of inguinal hernia. Both use reinforcement with interrupted fine silk or cotton sutures. Gaston divided the cord and removed the testicle in 11 out of 201 repairs. His recurrence rate was 1.7 per cent. Christopher and Penna reported 3.1 per cent recurrences. An extensive experience with the combination of the McArthur and the Halsted I technic in the repair of primary inguinal hernia at the Massachusetts General Hospital inspires confidence in this method.

Dennis and Varco<sup>8</sup> describe an excellent approach to strangulated femoral hernia. The sac is exposed through a vertical incision from the crease of the groin distalward. If the appearance of the sac wall gives the impression that gangrenous bowel is present, the sac is not opened. An oblique incision is then made 2 cm. above and parallel to the inguinal ligament, and the two incisions are joined in a T shape. The abdomen is opened, and the caught loop of bowel is divided between four clamps. The inguinal ligament is then cut across near its pubic attachment. The portion of the ligament forming the fibrous ring around the neck of the sac is left *in situ* as the remainder of the proximal ligament is freed. The entire sac with its contents is then gently removed, and an end-to-end anastomosis of the intestine is carried out. Repair of the defect

including the detached inguinal ligament, is effected with fine silk sutures. Ten cases are cited with 1 death from ruptured aortic aneurysm and 1 from cardiac decompensation. The majority of the wounds followed revealed no evidence of weakness or recurrent hernia.

Williams<sup>9</sup> makes a good appeal for the use of the Laroque abdominal approach for the repair of sliding hernia. The abdomen is opened through a McBurney-like incision within the usual long oblique inguinal wound. This allows adequate exposure for the reduction of the hernia and the suture of the stretched retroperitoneal colonic mesentery. This method may be more adaptable than the combined inguinal and abdominal approach advocated by Graham.<sup>10</sup>

Cases of herniation through the foramen of Winslow are reported by Gillis<sup>11</sup> and by Hamilton and Hardy.<sup>12</sup> Both patients were men and were admitted to the hospital with sharp onset of pain, of a severe and continuous nature, with vomiting. A pre-operative diagnosis of perforated duodenal ulcer was made in each case. Jejunum of considerable length was reduced after finger dilatation of the foramen. The case of Hamilton and Hardy required the suture of a rent in the bowel produced during reduction. No resection was necessary in either case, and both patients recovered.

### RETROPERITONEAL TUMORS

A good review of the literature with a study of 95 cases of retroperitoneal tumors occurring in the University of Iowa Hospitals in a twenty-year period is given by Donnelly.<sup>13</sup> Eighty-one per cent were malignant in the following order: undifferentiated neoplasm, fibrosarcoma and sarcoma. Three of the benign tumors recurred — one metastasizing to the chest thirteen years after the primary operation. Of the 81 patients explored, 16 died. Thirty-five per cent were resected, with 30 per cent recurrences either local or metastatic. The author believes that 77 per cent of such tumors are radiosensitive and therefore advises excision in addition to postoperative radiation when possible and radiation alone in the nonresectable tumors.

### THE LIVER

Kisner<sup>14</sup> reports 3 cases of solitary liver abscess treated by drainage and penicillin, with recovery. He discusses the possibilities of aspiration of the abscess cavity with the installation of penicillin. It appears that drainage offers better opportunity for a successful outcome. The characteristic picture of this disorder is represented by chills and fever, rapid weight loss, nausea and vomiting with pain in the hepatic region.

Thorck<sup>15</sup> presents an excellent description of the six subphrenic spaces where abscesses are prone to develop. Three of the spaces are subhepatic, and three are above the liver and are delineated by the

anatomic structures of the region. The diagnosis of the space involved is best determined by the clinical signs and lateral roentgenograms. Approaches to each space are suggested.

Three cases of successful resection of hepatoma are reported by Duckett and Montgomery<sup>16</sup>. One case recurred after six months, but the other patients were well at the time of the report. Hemorrhage was controlled by the mattress-suture method of Pickrell and Clay<sup>17</sup>. These sutures are placed through the normal liver tissue in an interlocking manner before the section to be removed is severed. Fibrin foam was helpful in 1 case in controlling the bleeding. Digital compression of the portal vein and the hepatic artery is useful in obtaining accurate hemostasis.

### THE SPLEEN

Hodge and Wilson<sup>18</sup> discuss benign cavernous hemangioma of the spleen. Thirty-one cases are collected from the literature. The authors believe that angiosarcoma, angioendothelioma, angioblastoma, simple sinusoid ectasia and so forth are included in some reports as cavernous hemangioma and are obviously not benign. Many of the reported cases were incidentally found at autopsy and had apparently been asymptomatic. Others caused pain from the huge tumefaction, and some of the spleens had ruptured, causing massive intraperitoneal hemorrhage. Hemangioma appears to be a tumor comprised primarily of new blood vessels, the anlage of which is thought to arise from vascular disarrangements. One case is reported in a thirty-five-year-old Negress who was admitted to the hospital with a huge, painful left-upper-quadrant mass. At operation the spleen was removed after the aspiration of 12,000 cc of bloody fluid. The total weight of the tumor was 13,130 gm, and its greatest diameter was 28 cm. The authors believe that this is the largest benign cavernous hemangioma of the spleen thus far on record. The patient made a good recovery from the procedure.

### THE PANCREAS

Shallow and Wagner<sup>19</sup> report a probable case of traumatic pancreatitis in a boy of eight who fell from his bicycle, landing on the handle bars in such a way that direct trauma to the abdomen occurred. The serum amylase was very high on admission, and this was the chief criterion for the diagnosis. Conservative treatment with large doses of penicillin resulted in cure. The authors discuss the problem and conclude that from 2 to 4 per cent of all cases of pancreatitis are of traumatic origin.

Tumors of the islets of Langerhans are reviewed by Lopez-Kruger and Dockerty<sup>20</sup>. In 10,314 routine examinations of the pancreas, 44 tumors were revealed. In the careful study of 500 pancreases by the authors, 8 tumors of the islet cells were found. This leads them to the obvious conclusion that such

tumors are usually symptomless and that hypoglycemia is a rare manifestation. When hypoglycemic symptoms occur, however, an attempt at medical management is justified. If this fails, the tumor must be excised. The authors state that 50 to 60 per cent of the tumors causing symptoms can be found and removed at the first exploration. Since the tumors are often multiple and the majority of them inactive, repeated operations are frequently necessary to relieve the patient. Resection of the tail of the pancreas will remove 50 per cent of the tumors. The body of the organ contains 20 per cent, and the remainder are found in the head. Only 1 or 2 per cent have an extrapancreatic location. Surgeons must be prepared to carry out procedures ranging from shelling out an easily accessible tumor to total pancreatectomy in patients who fail to be relieved by less extensive resections.

Marble and McKittrick<sup>21</sup> report 6 cases of islet-cell tumor of the pancreas with hyperinsulinism. Five patients had benign adenomas, and all of these were relieved. One patient had a mixed-cell type of carcinoma, with metastases to the liver, and succumbed seven weeks after operation. The lesions were found in the head of the pancreas in 4 cases and in the body in 1, and the malignant lesion originated in the tail of that organ. The authors stress early diagnosis and operation to avoid permanent central-nervous-system damage from repeated attacks of hypoglycemia and in the hope of cure when the lesion is malignant.

Carcinoma of the islets of Langerhans with hyperinsulinism is discussed by Sanchez-Ubeda and Carr<sup>22</sup>. Twenty-three cases are collected from the literature, and the detailed report of a case of their own is given. This occurred in a forty-year-old man, with typical attacks of hypoglycemia, who was brought into the hospital in coma. Death resulted, and autopsy revealed a primary carcinoma of the pancreas, with evidence of islet-cell origin. Metastatic lesions in the liver were microscopically identical with those found in the pancreas.

Most surgeons will agree with Pearse<sup>23</sup> that standardization of the Whipple operation for pancreaticoduodenectomy is necessary. The principles involved are end-to-end anastomosis of the common bile duct to the jejunum, anastomosis of the pancreatic duct to the side of the jejunum, with reinforcement by suturing the capsule of the pancreas to the wall of the jejunum, and anastomosis of the end of the stomach to the side of the jejunum. This logical plan directs pancreatic and stomach contents away from the liver so that ascending cholangitis is less likely to occur. It is natural that in the formative years of the development of this operation many ingenious modifications have been produced. Now that the procedure is done by so many surgeons, the standardization of the principles involved should be more universally adopted, with rare variations.

## APPENDICITIS

Meyer et al.<sup>24</sup> have analyzed the records of 5543 cases of appendicitis treated at the Cook County Hospital, Chicago, from 1928 to 1944. The mortality rate had decreased from 7.6 to approximately 4.0 per cent largely owing to the following factors: the nonoperative treatment of acute appendiceal abscesses, the more consistent use of the McBurney incision, and the omission of drainage of the peritoneal cavity. The advent of intravenous therapy and gastric suction, blood transfusion and antibiotics is stressed in order of common usage to account for the reduction in mortality.

Shullinger<sup>25</sup> has studied the results of the improvement in methods of treatment of acute appendicitis over a period of years at the Presbyterian Hospital in New York City. The mortality from 1916 to 1945 was 3.55 per cent. The last five-year average was 1.37 per cent, whereas for the year 1945 only, the rate was 0.43 per cent. Shullinger calls attention to the fact that local peritonitis has responded less favorably to modern methods of treatment than other complications of the disease.

McClure<sup>26</sup> reported that there had been no fatalities in 1089 consecutive cases of acute appendicitis in the past four years treated in the Henry Ford Hospital, Detroit. There had been a steady reduction in mortality from 0.92 per cent ten years ago up to the present time.

Hoerr<sup>27</sup> has evaluated progress in the treatment of acute appendicitis at the Peter Bent Brigham Hospital, Boston, for each five-year period from 1913 to 1945. There was little change for the better until the last period of his study, which comprised 382 cases with only 1 death. He concludes that sulfonamides acting systemically, gastric suction, the McBurney incision and the omission of drains are, in that order, responsible for the improved results.

Hurwitt<sup>28</sup> calls attention to the onset of acute appendicitis in patients undergoing treatment for other diseases. Ten such cases are collected from the records of the Mt. Sinai Hospital in New York City. He stresses the difficulty in making the diagnosis in such patients, owing to the concentration on the more obvious pathologic process for which the patient is being treated.

Mucocele of the appendix is discussed by Kirby,<sup>29</sup> who reports such a case in a forty-one-year-old woman who was admitted to the hospital with a diagnosis of acute appendicitis. The mucocele removed was 8.5 cm long and 5.5 cm in circumference. Kirby was able to collect 250 cases of this disease from the literature. The correct diagnosis is seldom made preoperatively and is usually made at operation for appendicitis, exploratory laparotomy or right hemicolectomy, or is an incidental autopsy finding. The results are good after appendectomy.

## THE GALL BLADDER AND BILE DUCTS

Congenital absence of the gall bladder is discussed by Latimer et al.<sup>30</sup> Seventy-one cases are collected from the literature. Thirty-eight of these were post-mortem findings, and 34 were discovered at operation. The authors report 3 cases from the Wesley Memorial Hospital, Chicago. They found that cholangiography was a reliable method of ruling out intrahepatic gall bladder.

Mahoney<sup>31</sup> reports 18 cases of cholecystoduodenocolic membranes encountered at the Strong Memorial Hospital, Rochester, New York. Most of these congenital bands have no pathologic significance, but a few may cause pain simulating cholecystitis or duodenal ulcer, or both. Some patients are relieved of symptoms after the division of the membranes. Mahoney believes that the reports in the literature regarding the incidence of 15 to 30 per cent are too high and that too much emphasis has been placed on their importance.

Daseler et al.<sup>32</sup> have studied the variations in the cystic artery in 500 specimens, finding twelve distinct patterns. This important anatomic contribution should be constantly borne in mind by surgeons. A good many of the catastrophes occurring during cholecystectomy are the result of unrecognized anomalies in this region. Abnormal distribution of the blood supply to the gall bladder and the liver is so commonly seen that too much emphasis cannot be placed on its surgical significance.

In two articles, Zaslow and his associates<sup>33, 34</sup> have reported the concentration of penicillin and streptomycin in the human gall bladder and the common hepatic duct. If the cystic duct is obstructed, the antibiotics will not reach the gall bladder. If the common duct is obstructed at the papilla of Vater, there is also lack of concentration of these agents in the hepatic ducts. In the absence of obstruction, the concentration was satisfactory in both series with the usual parenteral doses of the drugs.

Glenn<sup>35</sup> collected 17 cases of acute cholecystitis occurring in patients under treatment for other diseases in the New York Hospital in a period of fourteen years. He stresses the importance of an early diagnosis and operation in these cases because of the danger of gangrene and perforation. Symptoms are often attributed to nonsurgical complications or to conditions related to the original pathologic process. He considers it sound practice to study the condition of the gall bladder in all patients beyond the age of fifty who are about to undergo surgical procedures.

McGowan et al.<sup>36</sup> advocate a modified T tube for common-hepatic-duct drainage. A balloon is attached to the side of the long arm of the tube in such a manner as to prevent distortion of the common duct while the T tube is in place. By measuring, in millimeters of water, the amount of pressure within the duct that produces pain the authors be-

lieve that they can determine the optimum time for removal of the tube

Varco<sup>37</sup> has made a notable contribution in the treatment of pruritis in patients with certain chronic liver disorders. A small T tube is placed in the common hepatic duct as a permanent safety valve. Bile is allowed to drain to the outside for a few hours daily. Each patient may work out the amount of drainage necessary to maintain comfort. Varco believes that the itching is due to the concentration of bile salts in the blood serum and points out that 90 per cent of the bile salts excreted by the liver each twenty-four hours is reabsorbed from the intestine to be recirculated through the liver. Cholecystostomy was not effective in relieving these patients.

Incomplete removal of the cystic duct is thought by Hicken and his co-workers<sup>38</sup> to result in continued symptoms in cholecystectomized patients. They stress careful dissection of the cystic duct to near its junction with the common hepatic duct. It is important to leave no small stones or debris in the cystic duct. These authors consider more common use of cholangiography on the operating table to be of value in determining the length of the retained cystic duct and whether or not it is clear.

Womack and Crider<sup>39</sup> believe that from 5 to 20 per cent of patients continue to have symptoms after cholecystectomy. Reoperation on such patients revealed neuromas of the amputation type in 6 cases. Anatomic studies of the nerve supply to the region were made, and the authors conclude that careful denervation of the cystic duct should be accomplished in every cholecystectomy. The neuromas may be produced by scar tissue or trauma if the nerves are included in the tie with the cystic duct or with the cystic artery.

Lagerlöf<sup>40</sup> has relieved 14 patients of biliary dyskinesia by choledochal denervation. One patient was not improved by the same operation. He stresses the section of the nerves in the hepaticoduodenal ligament. After the operation, patients were given morphine and secretin simultaneously, and elevation in the serum amylase and bilirubin was less than that before operation with the same drugs. Lagerlöf believes that this test shows that the action of the sphincter mechanism of Oddi has been lessened by the procedure.

Grimson et al<sup>41</sup> have removed the celiac and supramesenteric ganglions in 4 patients with biliary dyskinesia. Three of the patients were relieved of their symptoms by this operation. A high subcostal incision is used, and the ganglions are exposed by division of the gastrohepatic omentum.

Smithwick and Chapman<sup>42</sup> have made studies in about 12 patients with biliary dyskinesia before and after right splanchnicectomy. Some of the patients have also had left lumbodorsal splanchnic resection. More than half of these patients have been relieved of their symptoms.

Smithwick<sup>43</sup> has also been successful in relieving severe pain in a patient with calcareous deposits in

the head of the pancreas by right lumbodorsal splanchnicectomy. This patient was rapidly becoming a morphine addict, and her pain was in every way similar to that of patients with biliary dyskinesia.

Petrov and Krotkina<sup>44</sup> have experimented with the production of carcinoma of the gall bladder in guinea pigs. Glass tubes, some of which contained a small amount of radium, were introduced into the gall bladders of 100 animals. Fifty-one of these lived over fourteen months, and of those 5 developed carcinoma of the gall bladder. Two were in the radium-tube experiments, but 3 were in the sterile-tube cases meant to be used as controls. It required from fourteen to thirty-nine months for these animals to develop carcinoma, 4 of them had metastases to other organs. The authors believe this to be supportive evidence that foreign bodies, such as stones within the gall bladder, predispose to the development of carcinoma of that organ.

Barnes and Zarr<sup>45</sup> report a case of papillary adenocarcinoma of the common hepatic duct localized above the entrance of the cystic duct. The lesion was excised, and a subtotal cholecystectomy was done. The remaining lower segment of the gall bladder was anastomosed end to end with the dilated but normal proximal portion of the common duct, a satisfactory re-establishment of continuity being thus obtained.

### THE STOMACH

Ransom<sup>46</sup> gives the statistical data on 1356 patients with gastric ulcer treated in the University of Michigan Hospital in a twenty-year period. Two hundred and forty-six patients were treated surgically, of whom 20 had acute perforation. One hundred and eighty-eight had gastric resections, and 38 had palliative procedures. The indications for operation were as follows: intractable to medical therapy, 36.7 per cent, possible carcinoma, 29.8 per cent, obstruction, 21.8 per cent, penetrating ulcer, 5.3 per cent, hemorrhage, 4.8 per cent, and question of perforation, 1.6 per cent. Ten and one tenth per cent, thought to be benign, proved on pathologic examination to be malignant, and 40 per cent of these were apparently cured. The over-all operative mortality was 7.9 per cent, most of the deaths occurring prior to 1936. Ninety-two per cent of the benign ulcers treated surgically had a satisfactory result. Four patients developed anastomotic ulcer, 3 of whom definitely had part of the pyloric antrum retained at the original resection, the other case was questionable in this respect.

O'Donoghue and Jacobs<sup>47</sup> review primary lymphosarcoma of the stomach. They cite Taylor's<sup>48</sup> report in 1939 of 152 cases collected from the literature with 5 from the Presbyterian Hospital in New York City. One hundred new cases are collected from the literature between March, 1937, and January, 1946. They add a patient of their own who was alive and well five and a half years after subtotal gastrectomy.

Radical surgery followed by radiation appears to give the best results in such cases

Coexistent duodenal ulcer and gastric cancer is discussed by Fischer et al<sup>49</sup> from the Mayo Clinic. Between 1911 and 1945, 45,000 patients with duodenal ulcer were seen. Forty-eight cases of gastric cancer were found in this group. This amounted to 1 case in 938, or 0.1 per cent. The acidity of the gastric contents was valueless in making the diagnosis of cancer in these patients, although 2 of them appeared with healed duodenal ulcer and achlorhydria. Nearly all the patients had changed or increased symptoms. Four of them had been previously operated on for duodenal ulcer. The average duration of stomach symptoms in the entire group was eleven years and four months. Results apparently better than those observed in the usual cases of gastric cancer were attributed to the fact that these patients were stomach conscious.

Boyce<sup>50</sup> gives credit to Laennec (1823) for the first report of acute perforation in gastric cancer. It is apparent that this common complication is rarely reported in the literature, since only 230 such cases have appeared. Thirty-six cases are included in Boyce's study; 3 patients were subjected to gastric resection, with 2 survivors. He agrees with Bigard and Overmiller<sup>51</sup> that this is the procedure of choice.

Hartnett<sup>52</sup> has made a collective study of 1405 cases of cancer of the stomach from the London hospitals for the years 1938 and 1939. Forty-nine and two tenths per cent were operated on, but only 17.3 per cent had resections. The operative mortality for patients treated radically was 32.9 per cent. Excluding the operative deaths, the five-year survival averaged 23.1 per cent. The average life of all patients, whether treated or not, was 27.4 per cent of normal, those resected before nodal involvement averaged 60 per cent, whereas those resected after nodal spread averaged 40 per cent of normal—a five-year life expectancy.

Abrahamson and Hinton<sup>53</sup> compare two series of cases of carcinoma of the stomach treated at Bellevue Hospital, New York City. In the first group, there were 2.2 per cent of possible cures, and in the second or later group, there were 5 per cent apparently cured. They stress the lack of progress in making an early diagnosis. They found little evidence to support the theory that benign ulcers change to cancer.

State et al<sup>54</sup> give a statistical review on 586 patients with cancer of the stomach seen in the University of Minnesota Hospitals in a ten-year period. Seventy-six and three tenths per cent were operated on, and 52.2 per cent had a resection. There were 276 partial and 31 total gastrectomies in the group. The operative mortality was 15.2 per cent in the partial and 30 per cent in the total resections, averaging 16.6 for the whole. This has been reduced from 25 per cent in 1936 to 4.9 per cent in 1945. Six and six tenths per cent of patients having resection

lived five years, this represents 21.5 per cent of those surviving the operation.

Pack, in discussing this paper, gave the figures on cancer of the stomach collected by McNeer at the Memorial Hospital in New York City. Six hundred and eighty-three patients were seen, and 79 per cent operated on. Thirty-five per cent had resections. The operative mortality was 12.2 per cent in the partial and 30 per cent in the total resections. There was a 34.7 per cent five-year salvage in patients surviving resection.

These figures coincide fairly well with those collected from the Massachusetts General Hospital by Welch and Allen<sup>55</sup>. The resectability is now about 50 per cent of all cases seen. The operative mortality has been reduced to 3 per cent for partial, but is still about 30 per cent for total gastrectomy. The transthoracic approach to tumors involving the cardia of the stomach, with extension to the lower esophagus, has increased the number of resections. The net five-year salvage has been raised from 5 to 7 per cent of all patients admitted. A more radical attitude in the treatment of gastric ulcer, because it is often impossible to distinguish a benign from a malignant lesion, will improve the cure rate. It was disappointing to find that patients do not appear for treatment earlier now than they formerly did.

Longmire<sup>56</sup> believes that total gastrectomy is the operation of choice in gastric cancer. He reports 20 cases treated in this manner, with 2 deaths. Seven patients were alive for more than a year and were eating well. Two patients had died of malnutrition after discharge from the hospital. He believes that such patients can be kept well on proper diet and so forth, and that those who have no appetite must be taught to eat regularly in adequate amounts.

It is quite obvious that the operative mortality for total gastrectomy can be reduced to a low level if all cases with cancer of the stomach are so treated. It is doubtful, however, that such a radical attitude is logical. It is admitted that a partial resection in many cases is inadequate. Recurrent disease, however, seldom appears in the remaining stomach segment. If one can obtain a good nodal dissection and transection of the stomach through normal tissue, the risk is reduced, and the patient is less apt to have nutritional difficulties and will probably have just as good a chance of cure as if the whole stomach had been removed.

Ransom<sup>57</sup> reports 60 cases of total gastrectomy at the University of Michigan Hospital between 1937 and 1946. Fifty-three patients had cancer, 4 benign ulcer mistaken for cancer, 2 lymphosarcoma, and 1 neurofibroma. Forty-eight patients survived the operation—a mortality of 23.3 per cent. Those who died of metastasis averaged ten and a half months of life. One patient was alive and well for seven years and eleven months, 1 for six years and one month, 1 for four years and five months, and 2 for one year and six months. Six patients—2

with recurrent disease — were alive from one to eight months

Gray, in a discussion of Ransom's paper, reported 124 cases of total gastrectomy at the Mayo Clinic with an over-all mortality of 40.3 per cent. This had been reduced to 16.6 per cent in the most recent 24 cases.

Smith<sup>58</sup> gives some interesting data on 89 patients subject to total gastrectomy at the Lahey Clinic. The mortality for the entire series was 29.1 per cent, which had been reduced to 16.3 per cent in the last 43 cases. He gives the life expectancy as follows: 50 per cent of patients will live twelve months, 28 to 38 per cent eighteen months, 16 to 29 per cent twenty-four months, and 9 to 21 per cent three or more years. Twelve patients lived three or more years. One was alive eight years and five months after a total resection for leiomyosarcoma, 1 for seven years and one month (having had lymphosarcoma), and 1 for five years and four months whose diagnosis was carcinoma simplex.

Lefèvre<sup>59</sup> and Orr<sup>60</sup> have reported modifications in esophagojejunostomy. Both transect the jejunum. Lefèvre closes both ends and does an end-to-side anastomosis after attaching the distal limb to the diaphragm posteriorly, then the proximal limb is sutured to the diaphragm in front of the esophagus and to the distal limb to protect the anastomosis. This is followed by a large stoma between the two jejunal limbs. Orr uses the distal closed limb of jejunum for an end-to-side hook-up with the esophagus and then implants the proximal jejunum into the distal limb at a low level after the method of Roux.

(To be concluded)

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 34101

#### PRESENTATION OF CASE

A twenty-one-year-old nulliparous housewife entered the hospital complaining of dyspnea of seven months' duration.

The patient was reported to have been a "blue baby" at birth and remained blue for several weeks. From then until the age of two years she was supposedly of normal coloring. At that time she had a spiking febrile episode without other symptoms, which was diagnosed as rheumatic fever. Thereafter she led a restricted existence and was never able to play with other children because of marked exertional dyspnea and cyanosis. During the ensuing fifteen years she had always had orthopnea requiring two pillows at night, frequent bouts of variable muscle and joint pains and seemingly unassociated episodes of spiking fever. Clubbing of the fingertips had been noted since an early age. During the past four years she had been followed in the Out Patient Department, where it was noted that she had a Grade IV systolic murmur, loudest in the second interspace to the left of the sternum. One year before admission she had some increased dyspnea and was thought to have slight neurocirculatory asthenia. Seven months before entry, following an emotional episode, she neglected her health and had another febrile episode, with a definite increase of cyanosis. She was hospitalized during a period of severe exertional dyspnea, the orthopnea requiring an increase from two to four pillows, hand and ankle edema, increased abdominal girth and epigastric pressure symptoms on effort. Two and a half months before entry she had a single episode of hemoptysis and hematemesis, followed by black stools for two days. Since that time she had been symptomatically stable, with less cyanosis, pain and edema but with fifteen brief episodes of shaking chills and frequent night sweats in the two weeks previous to entry.

Physical examination revealed a thin, dyspneic woman with marked cyanosis and clubbing of the fingertips. There was no edema or petechiae. The heart was enlarged, and the pulmonic second sound

was louder than the aortic second sound, there were a systolic thrill at the apex and a Grade IV precordial systolic murmur, a continuous low-pitched pulmonic murmur and a Grade II diastolic blow along the upper left border of dullness.

The temperature was 100°F, the pulse 108, and the respirations 26.

Examination of the blood revealed a red-cell count of 9,300,000, a hematocrit of 76, a hemoglobin of 24 gm per 100 cc and a white-cell count of 4500, with a normal differential count on several occasions. Urinalysis disclosed a specific gravity of 1.010 and a +++ test for albumin. The nonprotein nitrogen was 35 mg, the total serum protein 6.5 gm per 100 cc, with an albumin-globulin ratio of 1.64, and the chloride 105 milliequiv per liter.

X-ray examination showed the heart to be slightly diffusely enlarged, with a cardiothoracic ratio of 13/25, left auricular enlargement and some evidence of pulmonary fibrosis were demonstrated. The edematization rate was 0 mm per hour. The venous pressure was equivalent to 160 mm of water, and the circulation time sixteen to twenty seconds (arm to tongue). The vital capacity was 1.7 liter. Daily blood cultures failed to grow any organism either aerobically or anaerobically.

The electrocardiogram showed an enormous P wave in Lead 2, a very prominent P wave in Lead 3 and a PR interval of 0.18 second. Right-axis deviation was moderate. The T waves were low and upright in Lead 3 and upright in Leads 1 and 2 and CF<sub>1</sub>, CF<sub>2</sub> and CF<sub>3</sub>.

The hospital course, which lasted for three weeks, was remarkable only in that the daily temperature spiked to 100°F by rectum and to 102°F on the last three days. The dyspnea, orthopnea and cyanosis improved on bed rest for a while but became more marked in the last few days and were associated with some precordial-pressure symptoms, increased weakness and distress. The pulse rose to 120, the systolic blood pressure was maintained around 90 mm, with an indefinite diastolic level. Physical findings did not change appreciably, the lungs remained clear, and no peripheral edema appeared. The patient was placed in an oxygen tent on the twentieth hospital day. Penicillin therapy was begun. On the twenty-first day venesection of 500 cc of blood was done, with temporary relief of symptoms, but she suddenly stopped breathing and died that night.

#### DIFFERENTIAL DIAGNOSIS

DR. PAUL D. WHITE: I am glad to have been given this case, because I am sure that I shall learn something from it. I have never seen a case like this to follow through, although Dr. Mallory tells me that I did see this very patient some time ago when she was still living. I have, however, forgotten all about her. I am sure that I was as puzzled then regarding the actual answer as I am now.



One rarely sees a spiking febrile episode due to rheumatic fever under the age of three or four. This occurred in the case under discussion at the age of slightly over two years, and we must have some reservation about that episode. I do not know the cause. From the age of two the patient was very short of breath and cyanotic as she had been at birth. That restricted her activities very greatly. With the muscle and joint pains and fever, although they are not necessarily associated, we must think seriously of rheumatic fever, which, however, is a very rare complication of the *maladie bleue* in the first few years of life. The clubbing of the fingers and cyanosis coming on at birth make one think strongly, of course, of the tetralogy of Fallot.

The Grade IV systolic murmur is in keeping with the tetralogy of Fallot in which there is pulmonary stenosis. Sometimes there is a loud murmur and sometimes a relatively slight one, and rarely there is no murmur. So far the history fits the ordinary tetralogy of Fallot.

The latest febrile episode seven months before entry again makes one wonder about rheumatic fever or pulmonary infection.

The ankle edema and increased abdominal girth were probably due to venous congestion and engorgement of the liver on effort, which are evidence of total or right-sided heart failure.

The hematemesis may have come from swallowed blood. The hemoptysis is more important and must be ascribed to pulmonary infection, infarction or congestion, such as one sometimes encounters with mitral stenosis.

The shaking chill and the frequent night sweats are something else again. Rheumatic fever generally does not cause such symptoms, they strongly suggest a superimposition of bacterial endocarditis, in the absence of more definite evidence of pulmonary or other infection.

The marked cyanosis and clubbing of the fingertips on physical examination still remind one of the tetralogy of Fallot.

A continuous murmur if actually present must mean an arteriovenous shunt, almost certainly a patent ductus arteriosus. One may be fooled, however, by a continuous murmur at the base of the heart, which can be transmitted from the neck veins. The so-called venous hum is best heard in a child, this patient was no longer a child. The venous hum may be confused with the murmur of a patent ductus arteriosus. There are really no other conditions to be seriously considered in that region that give a continuous murmur.

Was the diastolic blow due to aortic or pulmonary regurgitation? We have seen it in the tetralogy of Fallot in 2 cases, in 1 with pulmonary stenosis and regurgitation, and in 1 with aortic regurgitation.

It is, however, very rare. The other findings — that is, the loud pulmonic second sound, the systolic thrill and the murmur — are not consistent with a diagnosis of uncomplicated tetralogy of Fallot. They are important clues and begin to lead us away from the ordinary uncomplicated tetralogy of Fallot.

The blood findings are characteristic of the morbus caeruleus or *maladie bleue*, of which the tetralogy of Fallot is the most common example. A good many other cyanotic congenital heart conditions, however, cause a polycythemia.

The albuminuria may be ascribed to renal congestion. The patient had congestive failure. An independent renal difficulty is possible, but less likely.

The left auricular enlargement and the pulmonary fibrosis demonstrated by x-ray examination are most extraordinary findings. Unfortunately the films have been lost. I wanted to make sure that there was really a large left auricle and not a right auricle, or some other part of the heart. That must be an important clue. Enlargement of the left auricle is not seen in the tetralogy of Fallot.

The pulmonary fibrosis is the second important clue. I wonder if there was any question between pulmonary fibrosis and pulmonary vascular congestion.

DR STANLEY M. WYMAN: I read the description, and the fibrosis was not so definitely stated. The observer believed that it might be congestion of the vascular shadows. We did think that there was left auricular enlargement, however.

DR WHITE: That was quite definite, evidently.

DR ISAAC TAYLOR: Our opinion was that the pulmonary findings on x-ray examination were mostly vascular.

DR WHITE: We do not see that in the tetralogy of Fallot, in which the lungs are undersupplied with blood and the left auricle is not large. The x-ray findings and the auscultatory data are very important clues.

How many cultures were taken?

DR LEWIS K. DAHL: I would say a minimum of twenty-one. They were all negative.

DR WHITE: The electrocardiogram showed an enormous P wave in Lead 2. It must have been one of the largest P waves ever seen. We see large P waves in cases of the tetralogy of Fallot and of auricular septal defect, but I do not believe that we have ever called them enormous. The P waves were also large in Lead 3. Right-axis deviation was moderate. That is important and one of the many clues, because with such prominent P waves as these associated with the tetralogy of Fallot or an auricular septal defect marked right-axis deviation should have been present.

Penicillin was finally begun despite the fact that no positive cultures were obtained. There had been a considerable delay, but at last — in desperation — penicillin was apparently used. Whether it

was begun because of the suspicion of subacute bacterial endocarditis or endarteritis or because an infection of uncertain cause was suspected, I do not know.

This is obviously a puzzling case. There are three important questions. In the first place, was this congenital heart disease with complications, or was it early rheumatic heart disease that might be traced back to birth or fetal life, if such a case ever occurs? I do not know that I have encountered or ever heard of a case of rheumatic heart disease present at birth. Was it rheumatic superimposed on congenital heart disease, or was it something entirely different?

In the second place, what structural defects were present to explain all the findings? Were there more than one? Do we have to make more than one diagnosis?

And thirdly, what was responsible for the febrile episodes and final fever and death? I cannot answer these questions with assurance but in attempting to answer them, I shall give my own opinions, which I am sure can be readily replaced by others.

In the first place, I favor congenital heart disease with complicating infection, which need not be rheumatic although the combination is very appealing because of the recurrence of the febrile episodes. I doubt the possibility of rheumatic heart disease alone without any congenital defects. Secondly, it seems to me that we must make one or the other of the diagnoses—congenital or rheumatic or the two together. I cannot imagine other types of heart disease in this case. Despite the early cyanosis and clubbing there are objections to the diagnosis, not only of the commonest cause of such signs—namely, the tetralogy of Fallot—but also of certain other defects behind a *morbus caeruleus*, such as Eisenmenger's complex, transposition of the great vessels, a single ventricle and tricuspid atresia, in the last of which left-axis deviation is the rule in the cases that are on record, instead of right-axis deviation such as that recorded here, tricuspid atresia is a clinical syndrome that now can be diagnosed as a result of Helen Taussig's work.<sup>1</sup>

Accentuation of the pulmonic second sound, the systolic thrill at the cardiac apex, the left auricular enlargement and the pulmonary fibrosis by x-ray study, as well as the enormous P waves, with only moderate right-axis deviation, in the electrocardiogram, are all contrary to what we expect to find in the tetralogy of Fallot, and most of them are contrary to what we expect to find in the other four less common types of the *morbus caeruleus* mentioned above. These findings by auscultation, x-ray examination and electrocardiogram seem to be most important clues. If we can fit them together they certainly point to mitral-valve deformity—probably stenosis and regurgitation. I do not remember having seen a patient with

congenital mitral stenosis, but I know that such a condition exists. In Maude Abbott's<sup>2</sup> 1000 autopsied cases of congenital heart disease there were 6 with a primary diagnosis of mitral stenosis. Equally rare or probably much rarer is rheumatic mitral stenosis in infancy, unless one can attribute congenital mitral stenosis to rheumatic infection in the fetus, with which I am not familiar. The continuous pulmonary murmur points strongly to a patent ductus arteriosus as a complication of whatever else this patient had. That is the commonest complication of congenital mitral stenosis in Abbott's cases, but I may be stretching a point. If we diagnose mitral stenosis, we can readily explain also the early dyspnea, the hemoptysis, and the "pulmonary fibrosis," which might be based on chronic pulmonary stasis. But how can we explain the high degree of cyanosis, the clubbing and the polycythemia? Severe chronic pulmonary stasis from birth might conceivably do that. Or is it not possible that a patent ductus arteriosus alone allowed a right-to-left shunt of venous blood directly into the aorta as the result of a high pressure in the pulmonary circulation? There was, to be sure, no mitral diastolic murmur, but cases of congenital mitral stenosis are already on record with only an apical systolic murmur.

Finally, was there rheumatism too, off and on, to explain the fever? I do not know. Or was it all rheumatism at an extremely early age? Or was there infection of other sort, recurrently, or quite possibly pulmonary infarction? Again, I do not know, but there was no proof thereof. Was there subacute bacterial infection involving the ductus or the pulmonary valve or even the mitral valve? That is also possible, but I find no proof. At the end penicillin was started quite likely with that possibility in mind.

Is it possible that an arteriovenous fistula in the left lung was responsible for the continuous pulmonary murmur instead of a patent ductus? Such a cause is very unlikely. The early diastolic murmur along the left sternal border could have been due to either slight aortic regurgitation (rheumatic) or relative pulmonary insufficiency secondary to the pulmonary hypertension, which is more likely, or to a remote primary lung disease.

In summary, my diagnoses are a congenital abnormality, with the *morbus caeruleus*, and with mitral-valve disease (stenosis), patent ductus arteriosus, pulmonary congestion, right-sided heart failure and recurrent infection (? rheumatic), with terminal subacute bacterial endocarditis or endarteritis or possibly rheumatic myocarditis.

DR TRACY B. MALLORY: Will you tell us what opinion was held on the ward, Dr Taylor?

DR TAYLOR: The only comment that I might make is in relation to the last few days of the patient's illness. She did not seem very ill throughout most of the hospital stay, except for an irregular

temperature, going up to 100 and 100.5°F daily until the last three days, when she became intensely cyanotic, and that progressed until her demise. With the progression of the cyanosis she became more and more lethargic. It was this change in her condition that prompted the giving of penicillin without bacteriologic diagnosis of endocarditis. Perhaps we delayed too long.

DR WHITE: It is still conceivable that there could be a shunt between the right ventricle and the aorta directly without supposing a reversal of flow.

DR BERTRAND WELLS: I should like to add two points. One was that the veins in the neck had large pulsations. These consisted of A waves and were almost synchronous with the abnormally large P waves of the electrocardiograms. The other point is that inside the apex there was a presystolic murmur. This was between the apex and the left sternal border, and it was doubtful whether this was in the mitral or the tricuspid area. I think that further phonocardiograms might have clarified this point.

DR WHITE: We might have to shift the stenosis from the mitral to the tricuspid valve on the basis of those findings (or add the two together).

#### CLINICAL DIAGNOSES

Subacute bacterial endocarditis, organism unknown

Congenital heart disease, type unknown

#### DR WHITE'S DIAGNOSES

Congenital heart disease morbus caeruleus

Mitral-valve disease (stenosis)

Patent ductus arteriosus

Pulmonary congestion

Right-sided heart failure

Recurrent infection (? rheumatic), with terminal subacute bacterial endocarditis, endarteritis or possibly rheumatic myocarditis

#### ANATOMICAL DIAGNOSES

*Congenital heart disease tetralogy of Fallot*

*Acute and chronic rheumatic endocarditis, with stenosis involving all valves*

#### PATHOLOGICAL DISCUSSION

DR MALLORY: The heart was one of the most remarkable that I have seen. There was congenital heart disease, which I thought was basically a tetralogy of Fallot: the pulmonary valve was stenotic, the interventricular septum showed a large defect at the base, there was dextraposition of the aorta, the right ventricle was markedly hypertrophied, and the left ventricle was small. The ductus arteriosus was a prominent fibrosed cord with dimpling at each end but not patent in its mid-portion. We thought perhaps it had become recently occluded within a period of a few months. In addition, all the valves of the heart were ab-

normal. There was a marked tricuspid stenosis, a pin-point mitral stenosis and a slight but significant aortic stenosis, with possibly a little aortic regurgitation. Vegetations were found on all valves. The vegetations were small, firm and characteristic of fresh rheumatic rather than bacterial vegetations.

The post-mortem cultures were sterile as were those taken during life. Microscopical examination showed almost no inflammatory reaction, although a trace of palisading was present at the base of two of the vegetations.

DR WHITE: Were there any Aschoff nodules in the myocardium?

DR MALLORY: None in eight blocks of tissue that were sectioned. A few minute fibrous scars were present, but they were not characteristic.

DR WHITE: Do you suppose that the rheumatic heart disease was superimposed on the tetralogy of Fallot?

DR MALLORY: Yes, I think that there is no other explanation of the picture. I do not believe that this many valves could have been congenitally stenotic.

DR WHITE: I do not believe so either.

DR TAYLOR: At autopsy I believe that an ante-mortem thrombus was found in the mitral valve.

DR MALLORY: There was a thrombus in the left auricle immediately above the mitral valve.

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- 2 Abbott, M. E. S. *Atlas of Congenital Cardiac Disease*. 62 pp. New York: American Heart Association, Inc., 1936.

#### CASE 34102

#### PRESENTATION OF CASE

A seventy-one-year-old woman, a retired clerical worker, entered the hospital with the chief complaint of abdominal pain and vomiting.

Six weeks before admission she was suddenly seized with severe abdominal pain to the left of the umbilicus and vomited almost at once. She was taken by ambulance to another hospital, where on conservative therapy the symptoms subsided and she was discharged ten days later. About once a week thereafter she had an attack of crampy, non-radiating pain to the left of the umbilicus that was accompanied by vomiting. The attacks lasted several hours. The present episode, which had begun eighteen hours before entry, started with pain, followed by vomiting, twelve hours before admission. The patient had not had a bowel movement for two days but had passed a little gas twelve hours before admission. On two occasions in the month prior to admission tarry stools were noted. For many years she had been slightly constipated, and there had been no recent change. There was no history of

intolerance to fatty foods, jaundice, urinary symptoms or previous gastrointestinal symptoms.

The past history was noncontributory except for a "shock" three years previously, resulting in a transitory hemiplegia. The patient had three children, one of whom had died of cancer at the age of forty-four.

Physical examination revealed a mildly dehydrated woman in moderately acute distress due to pain and vomiting. The heart and lungs were not remarkable. Marked tenderness was present to the left and slightly above the umbilicus, with referred rebound tenderness to this area. A mass was felt by one observer in this area, but its presence was not confirmed by others. Peristalsis was normal. Pelvic and rectal examinations were negative.

The temperature was 100°F, the pulse 88, and the respirations 20. The blood pressure was 170 systolic, 100 diastolic.

The urine gave a ++ test for albumin but was otherwise normal. Examination of the blood disclosed a white-cell count of 15,300 and a hemoglobin of 12 gm per 100 cc. A guaiac test on the stools was ++, but three subsequent specimens were guaiac negative. Twelve hours after admission the serum amylase was 23 units, the protein 5.9 gm, and the nonprotein nitrogen 25 mg per 100 cc, and the chloride 104 milliequiv per liter. The serum van den Berg was normal. A plain abdominal film showed several loops of moderately dilated small bowel and gas in a normal large bowel.

Conservative therapy was decided upon, and a Miller-Abbott tube was passed. The patient improved, the small bowel returned to normal size, and several days later a negative barium enema was done. Following this barium was given through the Miller-Abbott tube, which showed a 2.5-cm narrowing of the bowel distal to the tube. The lumen of the narrow portion was smooth and 4 mm in diameter. Two cholecystograms subsequent to removal of the Miller-Abbott tube showed no filling of the gall bladder.

Operation was planned for the fourteenth hospital day. On that morning the patient developed a temperature of 100.4°F, the highest since admission, and generalized crampy abdominal pain without vomiting. There was generalized abdominal tenderness, most marked in the right upper and lower quadrants. Peristalsis was normal and the white-cell count reached 30,000 (it had been 9000 three days before). Despite this, operation was performed as scheduled.

#### DIFFERENTIAL DIAGNOSIS

DR. S. PETER SARRIS: This is the case of a seventy-one-year-old woman with a relatively short history of abdominal pain. Six weeks before admission she had recurrent attacks of severe abdominal pain accompanied by vomiting, and no other attack except the one immediately preceding operation,

which was described as being in the left upper quadrant. She had been slightly constipated all her life, but she had no bowel movements for two days before the hospital admission. One gets the impression that the bowels began to move again while she was in the hospital, although there is no direct mention of this.

The past history was essentially noncontributory, except for a cerebral episode, which might influence us in our diagnosis as indicating a predisposition to vascular accidents. Physical examination was not particularly striking except for evidence of an inflammatory process in the left upper quadrant. She never ran much of a temperature; the temperature on admission was 100°F, and the highest recorded was on the day of operation, when it reached 100.4°F. Immediately preoperatively there was abdominal tenderness, more marked on the right side. The white-cell count initially was 15,000, but it went down to normal. Then on the day of operation it rose again to 30,000.

A plain film of the abdomen is reported as showing several moderately dilated loops of small bowel. When I read the history up to that point it was hard for me to see how the surgeons refrained from operation with an eighteen-hour story of acute small-bowel obstruction. In that interval we know that operation carries an extremely low mortality, I believe that the incidence is a little over 1 per cent. It seems apparent that some other diagnosis was considered, and the patient treated conservatively for reasons not apparent in the record. Then we come to what I think is the most important point in the protocol, so far as differential diagnosis goes: that there was a definite abnormality in the small bowel in the form of narrowing. I should like to ask Dr. Wyman to help us decide whether that abnormality was inflammatory, neoplastic or from outside pressure.

DR. STANLEY M. WYMAN: The first film shows a loop of small bowel in the left lower portion of the abdomen, running into the right lower quadrant, and a second loop low in the pelvis. There is gas in the cecum running up to the transverse colon, and there seems to be some gas in the descending colon. I can see no areas of unusual calcification or any definite soft-tissue masses. The chest films show no more than might be expected in any person of this age. The examination of the colon shows what is apparently a normal large bowel. The Miller-Abbott tube passed through several loops of small bowel down probably to the region of the lower ileum. After barium was introduced it ran through several loops of small bowel, probably ileum, and some filtered back proximally along the tube. These are the films that are probably more important; they show the area of narrowing in the small bowel, extending distally. The bowel is constantly narrowed on several films.

DR SARRIS Do you mean to imply that the narrow area did dilate finally?

DR WYMAN I do not know. It is not mentioned in the record, and not having done the examination, I cannot say. The appearance of the lesion makes me think that it did not dilate. If we are confronted with an area of constant narrowing it is of great importance to know about the mucosal pattern. I am not sure that I can see normal mucosal pattern throughout that area. There is a suggestion of some so-called shelving here, but that is unreliable.

DR SARRIS There is no chance that the shelving was produced by extrinsic pressure?

DR WYMAN It might be extrinsic constriction, rather than a mass compressing one portion of the bowel.

DR SARRIS Is there any evidence of a foreign body, such as gallstones?

DR WYMAN No.

DR SARRIS We come then to a differential diagnosis of what causes recurrent development of pain and vomiting and causes a small-bowel picture such as we have seen. I think that we have to assume one diagnosis, since I believe we can explain it on the basis of one diagnosis. However, I think that there are two diagnoses that could explain it. Pain in the left upper quadrant in recurrent attacks in a seventy-one-year-old woman suggests recurrent pancreatitis. The story fits fairly well except for the narrowing of the small bowel. I have seen narrowing like this in the distal transverse colon from pancreatitis with fat necrosis surrounding the transverse colon causing obstruction. I have also seen it in the duodenum in a case in which there was aberrant pancreatic tissue, but I have not seen it or heard it described in the ileum and therefore I believe we cannot consider that diagnosis seriously. The history sounds reasonable for gallstone ileus until one reaches the point where the area of narrowing is described. Six weeks before entry the patient had abdominal pain and was taken to a hospital, and at that time she may have had an acute gangrenous cholecystitis with perforation into the duodenum or a loop of small bowel, and within the next few weeks she had recurrent attacks of partial intestinal obstruction from the stone in the small bowel. The x-ray picture excludes that unless the gallstone had produced an ulcerative lesion in the area of the small bowel that later became stenosed, the stones meanwhile passing. That possibility is remote. Recurrent small-bowel obstruction from a band or a Meckel's diverticulum could produce a stenotic area like this, when the bowel became ischemic but never gangrenous enough to perforate. I have seen cases of chronic intestinal obstruction following an episode of acute intestinal obstruction with ischemia of the obstructed portion of the bowel followed by stenosis after the acute episode had subsided. That is why I was hoping to be told whether or not there was a shelf. There apparently

was not one. Certainly Dr Wyman will not commit himself definitely about whether or not there was a shelf. In almost all cases a shelf means a tumor, whereas lack of a shelf makes one think of an inflammatory lesion or an ischemic lesion.

We come down to two diagnoses that must be seriously considered. The first one is mesenteric thrombosis, although in view of the suggestion of a shelf it might be less seriously considered. All patients with mesenteric thrombosis are not operated on, nor do they necessarily die without operation. We know of cases that have been explored, a thrombosis found, which was too extensive to resect, and the patient sewed up with recovery. We also know that thrombosis can produce localized areas of ischemia without perforation. I remember a case in which the patient had resection for mesenteric thrombosis, and three weeks later developed small-bowel obstruction naturally assumed to be due to faulty anastomosis, but on reoperation the anastomosis was found to be perfect, although an area of stenosis distal to the anastomosis had been produced, presumably by ischemia in that area, without complete necrosis. This picture could have been produced by mesenteric thrombosis six weeks previously, with a resultant small area of ischemia. As the bowel was stenosing down recurrent bouts of abdominal pain and vomiting occurred. Then there was the last episode of recurrent intestinal obstruction because the tube was removed, or what is more likely, another more massive attack of mesenteric thrombosis. It is well known that mesenteric thrombosis causes such recurrences.

How about regional enteritis? I should have mentioned that earlier. Isolated areas of stenosis like this do occur in regional enteritis, but I think that the patient was too old for that diagnosis.

Regarding tumors, we have sarcoma, carcinoma and carcinoid to consider. In general the picture fits very nicely with small-bowel tumor. The age is correct because the lesions tend to occur in that age group. The recurrent attacks of intestinal obstruction and vomiting, the crampy pain, the suggestion of two tarry stools—one cannot place too much reliance on the history of the two tarry stools as given by the patient—and the bleeding all occur in small-bowel tumors. The story is consistent. The final episode could have been perforation of a carcinoma or a sarcoma of the small bowel. Malignant tumors of the small bowel often perforate and produce peritonitis. If it is a tumor, of course, in general the higher up in the small bowel the more apt it is to be carcinoma, and the lower down, sarcoma. A carcinoid that one usually associates with the appendix often occurs in the small bowel, more often in the terminal ileum than anywhere else in the bowel. Carcinoid does not bleed as most malignant small-bowel tumors do. Twenty-five or 30 per cent of carcinoids of the small intestine

are often malignant as against those that occur in the appendix, which are seldom malignant.

My first choice of diagnosis in this case is a malignant tumor of the small bowel, and since it is in the lower part I can go a step farther and say sarcoma with perforation. The other distinct possibilities are any other small-bowel tumor and mesenteric thrombosis.

DR TRACY B. MALLORY: Can you tell about the opinion on the ward, Dr. Raker?

DR J. W. RAKER: There was a great deal of discussion and difference of opinion, particularly regarding the management of this patient. As Dr. Sarris suggested there was a strong feeling that she should have an operation on the day she was admitted. However, with the past history of earlier episodes and the fairly recent attack that had subsided spontaneously and the upper abdominal signs, our diagnosis that night was a possible acute pancreatitis, although there was a difference of opinion about that. Subsequently, further investigation revealed a lesion in the small bowel, and the majority of us believed that she had a small-bowel tumor and chronic cholecystitis. I believe that that was Dr. Linton's diagnosis when he explored her. The episode of pain during the last night on the ward was not particularly remarkable, and we totally missed the secondary diagnosis that was discovered.

#### CLINICAL DIAGNOSES

Small-bowel tumor  
Chronic cholecystitis

#### DR. SARRIS'S DIAGNOSIS

Malignant tumor of small bowel, with perforation immediately preoperatively

#### ANATOMICAL DIAGNOSES

*Carcinoma of gall bladder, with extension to small intestine*  
*Acute gangrenous appendicitis, with perforation and abscess formation*

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Will you continue with the operative findings, Dr. Raker?

DR. RAKER: Dr. Linton explored the patient and discovered that she had a chronically inflamed gall bladder containing stones, which was the site of an inoperable carcinomatous process involving the liver. The lesion in the small bowel was caused by peritoneal implants on the surface of the small bowel, which had partially encircled the lumen. An unexpected finding was the presence of a perforated appendix with abscess formation in the region of the appendiceal mesentery and the mesentery of the small bowel. The loops of the small bowel involved in carcinoma were resected. It was impossible to do anything to the gall bladder. The appendix was removed, and the abscess in the region of the small-bowel mesentery was drained. Unfortunately, the wound became infected in spite of delayed closure and finally after a long period healed. However, the appendiceal abscess went on to form a large mass in the right lower quadrant that was easily palpable in the pelvis, and it was necessary to do an incision and drainage of the abscess. This was done through the right lower quadrant, and a large cavity was found and drained. The patient recovered from that and left the hospital to go to a convalescent home. We were glad that she was able to do so.

DR. MALLORY: The specimens that we received were biopsies from the carcinomatous gall bladder and two segments of small bowel, each of which was markedly obstructed by a nodule of tumor. In one of these nodules the tumor had grown through the bowel wall all the way from serosa to mucosa, and there was an ulceration of the latter. It is quite likely that the story of tarry stools and hemorrhage from the bowel was correct, though one does not expect a secondary tumor of the bowel to cause hemorrhage.

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## TOTAL TRANSECTION OF THE SPINAL CORD

ATTENTION is directed to an article on the occurrence of extensor spasm in patients with a transected spinal cord printed elsewhere in this issue of the *Journal*. As the authors note, this neurophysiologic phenomenon was first given the attention it deserved outside of the experimental laboratory by Head and Riddoch. These investigators studied 8 such patients who had sustained their injuries in World War I. Their observations are authoritative and classic. They were unknowingly handicapped, however, by their inability to control urinary-tract sepsis, by their necessary lack of knowledge of the effect of proteinemia, by the confusing side effects produced by the spasm.

by the short life span of their patients. Their interpretations, moreover, were undoubtedly strongly influenced by the fundamental experimental work along these lines that had been done on animals by such a master physiologist as Sherrington.

All these circumstances combined to paint in the minds of the medical profession a picture of the response in man to accidental transection of the spinal cord that corresponded exactly with that found in experimental transection in animals. Thus it was taken for granted that after the subsidence of spinal shock all patients with transected cord would exhibit involuntary flexor as opposed to extensor spasms of the lower extremities. Spinal sweating and certain visceral manifestations, notably those affecting the urinary bladder, were thought to be associated constantly with these spasms. As a corollary the presence of involuntary extensor as opposed to flexor spasms was considered diagnostic of the less damaging partial injury of the cord and hence to warrant a better prognosis. The present authors present evidence that such a distinction, however true it may be in animals, does not hold true in man.

The fundamental studies that enabled Macht and Kuhn to collect their data have a distinct Boston tinge. Although the classic work that demonstrated the details of the activities of the normal bladder was done in London, England, one of the authors has since attached himself permanently to the Neurological Unit of the Boston City Hospital. With this work as a background there then was developed in the Neurosurgical Department of the same hospital a more accurate understanding of the mechanisms governing the spinal bladder, together with a method of treatment that reduced the mortality caused by the genitourinary-tract infection in these patients from 75 to 15 per cent.<sup>2</sup> Following this, attention was called in 1940 to the importance of a high-protein diet if the treatment of bed sores was to succeed.<sup>3</sup> This virtually abolished the other great cause of the mortality and morbidity that had been considered an indispensable accompaniment of the care of these patients. It was now possible to approach directly the problem of the "spasms." Anterior dorsolumbar rhizotomy eliminated this distressing complication and in

addition yielded extra dividends not only in the form of prolongation of life and quicker healing of bed sores but also in the possibility of ambulation and a satisfactory social life. This work, too, was all initiated and carried out at the Boston City Hospital and has since been repeated and independently confirmed at other civilian and army neurosurgical centers.

These methods were supplemented by the providential discovery of the sulfonamides and the antibiotics and, aided by the widespread use of frequent blood transfusions, saved the lives of many wounded men who would otherwise have died during their first year after wounding. Thus, for the first time a significant number of men with spinal-cord transections that were uncomplicated by infection and debility have become available for neurophysiologic observations that are comparable with the earlier similar observations hitherto limited to experimental animals. The paper by Macht and Kuhn is believed to be the first report that has been made under such properly controlled conditions in man and that deals with these fundamental responses to what amounts to an experimental injury.

It should be encouraging to those members of the profession who have neither the opportunity nor the inclination to delve into pure research and who are discouraged by the attitude of amused tolerance with which the laboratory worker regards the efforts of the practitioner to add to the sum of medical knowledge, to learn that in this instance, at least, the physiologist has been successfully challenged by the clinician. The latter has, moreover, provided as a bonus for his subjects' longer life, less sickness, hitherto unattainable ambulation and the rehabilitation of some of those to whom the world owes a great debt of gratitude.

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#### "UNNECESSARY OPERATIONS"

THAT the medical profession has been guilty, wittingly or unwittingly, of ill advised therapeutic measures is common knowledge. Errors in judgment and errors caused by ignorance or misinterpretation of the patient's condition will always occur. It is the aim of physicians to reduce these costly mistakes to the lowest possible level.

In the endeavor to combat and to minimize such unnecessary operations as have been discussed by a well known popular writer in the *Woman's Home Companion*<sup>1</sup> and later abstracted for one of the foremost monthly digests,<sup>2</sup> it is perhaps inevitable that overenthusiastic and even inaccurate statements may be made. One deplores, however, such statements as the one made by a pediatrician that acute appendicitis is a rare disease in childhood but, unfortunately, appendectomy is a 'common operation'.

It is to be feared that such a statement may do a great deal of harm in the campaign so earnestly forwarded for early recognition and treatment of acute appendicitis in childhood. Only a few years ago, in Massachusetts, acute appendicitis stood high on the list of causes of death in children from one to twelve years of age. If the infant survived his first year his greatest risks before the age of twelve came from contagious disease, pneumonia, automobile accidents, and acute appendicitis, in that order, and the patients dying of acute appendicitis, almost without exception, were those in whom the disease had been unrecognized until after the appendix had ruptured and peritonitis was well established.

In the condensed article, appearing in the digest, there is a heading signed by a professor in one of the leading medical schools in the East stating "[The author] is absolutely correct in his statements. I am in favor of establishing every safeguard he mentions and many more besides."

One agrees heartily with most of the opinions expressed in this article, and perhaps necessary reform will come only as a result of overenthusiasm in presenting the facts. One regrets, however, to see a blanket statement, such as the above that the article is absolutely correct in all its observa-



Malaria was reported from Weymouth, 1, total, 1  
 Meningitis, meningococcal, was reported from Boston, 2, Brookline, 1, Cambridge, 1, Fall River, 1, Lowell, 2, Methuen, 1, North Brookfield, 1, Northampton, 1, total, 10  
 Meningitis, Pfeiffer-bacillus, was reported from Cambridge, 1, Malden, 1, Springfield, 1, Watertown, 1, Worcester, 1, total, 5  
 Meningitis, pneumococcal, was reported from Chicopee, 1, Methuen, 1, Newburyport, 1, Springfield, 1, total, 4  
 Meningitis, undetermined, was reported from Lakeville, 1, Pittsfield, 1, Quincy, 1, total, 3  
 Poliomyelitis was reported from Lowell, 1, total, 1  
 Salmonellosis was reported from Brockton, 1, Malden, 1, New Bedford, 1, Salem, 1, total, 4  
 Septic sore throat was reported from Boston, 3, Falmouth, 2, Fitchburg, 1, Mansfield, 1, Tewksbury, 1, total, 8  
 Tetanus was reported from Shrewsbury, 1, total, 1  
 Trachoma was reported from Malden, 1, total, 1  
 Trichinosis was reported from Boston, 1, Fall River, 4, Malden, 2, total, 7  
 Typhoid fever was reported from Boston, 1, Lynn, 1, total, 2  
 Undulant fever was reported from Hopedale, 1, Hopkinton, 1, total, 2

## MISCELLANY

### BAY STATE NURSERY SCHOOL

The Bay State Society for the Crippled and Handicapped, in co-operation with the Boston Visiting Nurse Association, Cerebral Palsy Council of Boston, The Children's Hospital, Crippled Children's Services, Massachusetts Department of Public Health and Massachusetts General Hospital, has established a demonstration school for children with cerebral palsy at 355 Boylston Street, Boston

Twenty educable children from four to eight years of age will be accepted, following an assessment of their particular needs in relation to cerebral palsy. The school will provide physical and occupational therapy, speech instruction and parent education

## BOOK REVIEWS

*Encyclopedia of Endocrinology* Section IV Ovary Volume VII in two volumes, *Ovarian Tumors and Bibliography* By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Can.), professor and director of the Institute of Experimental Medicine and Surgery, University of Montreal 4°, cloth, 289, 427 and 60 pp., with 38 plates Montreal Richardson, Bond and Wright, 1946 \$21.75

This monumental work, a small part of a general work on endocrinology of ten contemplated sections, is based on the author's library of approximately 250,000 items (reprints, abstracts, microfilms and books). The volume *Ovarian Diseases Other than Tumors* has been prepared for publication, and it is hoped that it will appear in the near future. This volume on ovarian tumors is published in two parts—text and bibliography. The text discusses in a critical manner the existing relevant literature on ovarian tumors. The subject is divided into the following sections: ovarian and paraovarian tumors in general, endocrine tumors, chorion-epitheliomas, common cysts, common carcinomas, "mesonephromas" and "Brenneromas," endometriosis, teratoids and non-epithelial tumors. The text on classification presents the schemes of Goodall, Cornill, Schiller, Novak, Miller, Geist, Taylor and that of the author used in this work. The material is well organized, written and illustrated. A good index and a list of periodicals and serials conclude the volume. The bibliography consists of approximately nine thousand references. The printing is excellent and the binding is of the loose-leaf type. The work is recommended for all medical libraries as a fundamental reference source.

*Adjustment to Physical Handicaps and Illness: A survey of the social psychology of physique and disability* By Roger G. Barker, Beatrice A. Wright and Mollie R. Gonick. 8°, paper, 372 pp. New York: Social Science Research Council, 1946 \$2.00

In this monograph the authors have brought together in a single volume what is known of the relation between social behavior and personality and the normal variation in physical size, strength, motor ability, sensory acuity and health. They have endeavored to evaluate present knowledge in the field of somatopsychology and to point out the way for future investigation. The various chapters of the text discuss the somatopsychologic aspects of normal variations in physique, the significance of crippling and impaired hearing, the social psychology of the tuberculous patient and of acute illness and the employment of the disabled. The bibliography consisting of fifty-three pages covers the various aspects of the subject discussed in the text. Two indexes of authors and subjects conclude the volume. The material is well organized, and the printing is well done with a good type on good paper. This monograph is recommended for all medical, social and general libraries. The price is surprisingly low.

*Tomorrow's Food: The coming revolution in nutrition* By James Rorty and N. Philip Norman, M.D. With a foreword by Stuart Chase. 8°, cloth, 258 pp. New York: Prentice-Hall, Inc., 1947 \$3.50

In this book a journalist and a physician have collaborated to write a history of modern diet and nutrition. The text is presented in an interesting narrative style and devotes special chapters to outstanding incidents the world over in the field of diet, principally among the so-called "common people." Their thesis is that most of the malnutrition troubles of today are due to the processing of wheat into white flour and brown sugar into white, and the use of canned milk. Their forecast for the future is bright, placing reliance on the great advances in technology, especially in food processing resulting in dehydration, the freezing and synthesizing of foods and the fortification of foods with synthetic vitamins.

Cheshire, England, lived for twenty-five years under the National Health Insurance Act. At the end of this period the six hundred panel doctors appointed a committee to determine whether the act had fulfilled its objective of "the prevention and cure of sickness." The committee and the body of physicians were unanimously convinced that on the question of cure there had been success, for the average expectancy of life had risen since the passage of the act. On the question of prevention there was positive failure, since the evidence was clear to these doctors that the illness in the community resulted from a lifetime of improper nutrition. Anemia of mothers and infants, bad teeth, rickets and constipation were prevalent. They attributed these ills to constant lifetime use of white bread, tinned salmon and dried milk. Likewise is told the stories of the Indian tribe of Hunzas and the world-wide travels of Dr. Weston A. Price in search of a people with good teeth. Wherever he found white flour, granulated sugar and canned foods, he found decayed teeth, where the diets were of natural unprocessed foods, the teeth generally were found to be in good condition without appreciable decay. The experience of the first draft for World War II revealed that 25 per cent of the first million men selected were rejected because of defective teeth, second only to poor eyes in causes for rejection. Special chapters deal with the processing of flour, sugar, milk and butter. The vitamin propaganda is frankly discussed.

The last part of the volume discusses food production from the point of view of agricultural research and distribution from the consumers' side of the question. The authors have produced an interesting book worthy of serious reading. It should find a place in all medical and public libraries.

*Textbook for Psychiatric Attendants* By Laura W. Fitzsimmons, R.N., M.A. 8°, cloth, 332 pp. New York: The Macmillan Company, 1947 \$3.50

This textbook was written primarily for attendants in mental hospitals. The text is divided into two parts. The first discusses topics of a general character, including special problems such as suicide, the use of restraint, diet, emergencies and first aid, ward housekeeping, hygiene and health, nursing care according to group classification and special therapies. The second part is given up to treatment and procedures, with a chapter on psychiatric definitions and explanations. A list of books for further reading is appended to the text. The book is well written and well published and should prove valuable to those for whom it was written.

*Tutoring as Therapy*. By Grace Arthur Ph.D. 8 cloth 125 pp. New York: The Commonwealth Fund 1946 \$1.50

This monograph discusses the individual teaching of young children of normal intellectual capacity but maladjusted because of a lack of adequate teaching at the lower grade levels, or because of some special disability prolonged illness an emotional or adjustment problem or because of some personal idiosyncrasy. The author describes her early experimental work with first grade pupils conducted in St. Paul. Other chapters have to do with the selection training and supervision of tutors, methods used to remedial teaching and tutoring as a community project. Two chapters are devoted to the discussion of a large number of illustrative cases. The material is well organized and the volume is well published in every way. This monograph should be in all school and general libraries and should prove valuable to psychologists and pediatricians.

## BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Dermatologic Clues to Internal Disease*. By Howard T. Behrman M.D., assistant clinical professor of dermatology, New York University College of Medicine adjunct dermatologist Mount Sinai Hospital and Beth Israel Hospital and associate dermatologist Hillside Hospital. 8 cloth 165 pp. with 118 illustrations. New York: Grune and Stratton 1947 \$5.00

The material in this small book is arranged alphabetically under the names of constitutional diseases exhibiting associated skin changes. The descriptions are brief and are illustrated in a large number of cases. Skin diseases of significance or of diagnostic aid in internal medicine are included, but the common skin diseases and the exanthems are excluded. The monograph is written to supply the apparent need for the correlation of skin disorders with visceral dysfunction. The price seems excessive for the size of the book despite the large number of half tones.

*A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears*. By Olive Gates M.D. pathologist Massachusetts State Tumor Diagnosis Service and assistant pathologist, Pondville Hospital (Massachusetts Department of Public Health) and Shields Warren M.D. assistant professor of pathology Harvard Medical School pathologist New England Deaconess and New England Baptist hospitals and reserve consultant in pathology to the Bureau of Medicine and Surgery United States Navy Captain (M.C.) U.S.N.R. With a foreword by George N. Papanicolaou M.D., Ph.D. associate professor, Department of Anatomy and research associate, Department of Obstetrics and Gynecology Cornell University Medical College and New York Hospital. 4 paper 182 pp. Cambridge Massachusetts: Harvard University Press 1947 \$4.00

The authors have prepared this handbook as a laboratory guide especially for pathologists who are interested in the vaginal smear test for cancer and find it necessary to instruct themselves in the procedure. The material is well arranged and discusses the technique of the method and its application to suspected cases. There are valuable chapters on sources of error in diagnosis and on a current appraisal of the method. The text concludes with a bibliography of current literature. An atlas of fifty plates of benign cells and malignant cells is appended to the text. The plates are exceptional in quality. The offset printing is good. This handbook should prove valuable to all physicians interested in the method.

*List of File Microcopies*. By the United States National Archives. 4 paper 31 pp. Washington D.C. The National Archives of the United States 1947 Free

In 1940 the archivist of the United States began the micro filming of important records in his care and to May 31 1947

one thousand nine hundred and eighty seven rolls of master negatives had been completed. Positives of any of these films may be had at cost from the National Archives. There has as yet not been developed any comprehensive plan and most of the microcopies have been made on special request for particular records. Some of the records already copied date back to 1790. The primary objective of the program is to make available important records to investigators at a distance from Washington. To date there have not been copied any records of medical significance although certain records of the Bureau of the Census are available.

*Ilustraciones Obstetricas*. By Doctores Gerardo Will y adjunto del Instituto de Anatomia Patologica (director M. Ascanazy) de la Universidad de Ginebra medico anatomista patologo de la Casa Municipal de Maternidad Concepcion Palacios, Caracas investigador en la Facultad de Medicina Instructor de la cátedra de Histologia Normal de la Universidad Central de Venezuela and Oscar Aguero medico-partero adjunto del Servicio No. 2 de la Casa Municipal de Maternidad Concepcion Palacios Caracas. Prologo por el Doctor Leopoldo Aguerrevere, profesor de clinica obstetrica de la Universidad Central de Venezuela. 4 paper 46 pp. Caracas: Casa municipal de Maternidad Concepcion Palacios, 1946.

This pathological atlas of obstetric conditions is based on 4,000 patients admitted to the maternity hospital in Caracas. It is the role of the hospital in perform autopsies on fatal cases resulting in a wealth of material suitable for teaching purposes. The plates are made from photographs and are in scale. The selection of subjects is good and the reproductions are exceptional. Many rare conditions are depicted: microcephalocele hydrocephalus with microcephalocele hydrocephalus, Ritter's and Werlhof's diseases hydatidiform mole, uterine rupture compression of the fetus and others, totaling twenty two pathologic conditions. The first plate is of a gravid uterus, showing the normal insertion of the placenta. The original specimens are preserved in the museum of the hospital. This fine atlas is worthy of a place in all medical libraries and should prove of interest to obstetricians.

*Medical Care and Costs in Relation to Family Income: A Statistical Source Book*. Selected and compiled by Helen Hollingsworth Margaret C. Klem and Aona M. Baney. Bureau Memorandum No. 51 Second edition 4 paper 349 pp. with 317 tables. Washington D.C. Federal Security Agency Social Security Administration Bureau of Research and Statistics 1947 \$1.25

This second edition contains the same material on the basic data on illness and the cost of medical care that were contained in the first edition. Sections on the economic characteristics on vital statistics health personnel and facilities and voluntary hospital and medical-care insurance have been added. This reference work should be in all public health and medical libraries.

## NOTICES

### JOSEPH H. PRATI DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall 9-10 a.m.

#### MEDICAL CONFERENCE PROGRAM

- Friday, March 5—Pitfalls of Roentgenologic Diagnosis  
Dr. Merrill Sosman  
Wednesday, March 10—Some Aspects of the Unipolar  
Extremity Leads of the Electrocardiogram. Particularly  
with Regard to the Q Problem. Dr. Heron Macdonald  
and Lester Joseph  
Friday, March 12—Factors in the Production of Acute and  
Chronic Severe Liver Disease. Dr. Charles S. Davidson  
Wednesday, March 17—Pediatric Clinicopathological Con-  
ference. Drs. James M. Baty and H. E. MacMahon  
Friday, March 19—Some Aspects of Auscultation of the  
Heart. Dr. Samuel Levine

Wednesday, March 24 — The Etiology of Simple Goiter

Dr Monte A Greer

Friday, March 26 — The Distribution of Amino Acids between Cells and Extracellular Fluid Dr Halvor Christensen

Wednesday, March 31 — Radioactive Phosphorus Therapy  
Dr Bruce Brown

On Tuesday and Thursday mornings from 9 00 to 10 00 Dr S J Thannhauser will give medical clinics on hospital cases. On the second and fourth Friday afternoons of each month therapeutic conferences will be held from 2 00 to 4 00 with round-table discussion, Dr R P McCombs, moderator, Dr Merrill Sosman will conduct x-ray conferences from 4 00 to 6 00. On Saturday mornings from 9 00 to 10 00 clinics will be given by Dr William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12 00 to 1 00.

All exercises are open to the medical profession

## BOSTON CITY HOSPITAL

### HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital will present a lecture in its Tuesday evening lecture series in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital, on Monday, March 8, at 7 p m. Dr Frank Horsfall will speak on the subject "Primary Atypical Pneumonia."

All interested persons are cordially invited to attend

## AMERICAN CONGRESS OF PHYSICAL MEDICINE

The spring session of the Eastern Section of the American Congress of Physical Medicine will be held at Jefferson Medical College, Philadelphia, on Saturday, April 10, at 2 p m.

There will be a symposium on the "Effect of Physical Inactivity and of Exercise" in the afternoon and a round-table discussion on "Low Back Pain and the Sciatic Syndrome" in the evening at Benjamin Franklin Hotel.

## SUFFOLK CENSORS' MEETING

The censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, on Thursday, May 6, at 4 p m.

## AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC

The general oral and pathology examinations (Part II) for all candidates will be conducted in Washington, D C, by the American Board of Obstetrics and Gynecology from Sunday, May 16, through Saturday, May 22. The Shoreham Hotel in Washington will be the headquarters. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by direct application in writing to the Shoreham Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's office not later than April 1.

Candidates in military service are requested to keep the Secretary's office informed of any change in address.

Applications will be received until November 1, 1948, for the 1949 examinations.

For further information and application blanks address Paul Titus, M D, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

## INTERNATIONAL CONGRESS ON MENTAL HEALTH

An International Congress on Mental Health will be held in London, England, from August 11 to 21, 1948. The Congress will consist of three international conferences: "Child Psychiatry" (theme, personality development in its individual and social aspects with special reference to aggression), "Medical Psychotherapy" (theme, guilt)—these two

conferences will run concurrently from August 11 to August 14 and "Mental Hygiene" (theme, mental health and world citizenship), which will run from August 16 to August 21. The last conference will form the major part of the program. The following subdivisions of the general theme will be the main topics on consecutive days: problems of world citizenship and good group relations, the individual and society, family problems and psychological disturbance, planning for mental health (organization, training, propaganda), mental health in industry and industrial relations, and concluding session and summaries.

This conference is sponsored by the International Committee for Mental Hygiene, Inc, 1790 Broadway, New York 19, New York.

## REFRESHER COURSES FOR OFFICERS OF THE NAVY MEDICAL CORPS RESERVE

Refresher courses in medicine, surgery, obstetrics and gynecology, for reserve officers of the Navy Medical Corps, will begin at Chelsea Naval Hospital on March 28. The courses will be of two weeks' duration, the final period ending in May. Full pay and allowances in grade will be paid for the two-week period of active duty. Quarters are not available at the hospital and must be arranged for privately. Thirty medical corps officers will be admitted to each two-week period.

The refresher program will be supervised by the regular staff of the hospital, augmented by the consulting staff.

Applications for participation in the program should be mailed to District Medical Officer, First Naval District Headquarters, Navy Building, 495 Summer Street, Boston 10, Massachusetts.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 11

#### FRIDAY, MARCH 12

\*9 00-10 00 a m Factors in the Production of Ascites and Edema in Severe Liver Disease Dr Charles S Davidson Joseph H Pratt Diagnostic Hospital

\*10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital

12 00 m-1 00 p m Clinicopathological Conference (Boston Floating Hospital) Joseph H Pratt Diagnostic Hospital

#### MONDAY, MARCH 15

\*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital

#### TUESDAY, MARCH 16

12 00 m X-Ray Conference Margaret Jewett Hall, Mt Auburn Hospital, Cambridge

\*12 15-1 15 p m Clinicoradiological Conference Peter Bent Brigham Hospital

\*1 30-2 30 p m Pediatric Rounds Burnham Memorial Hospital for Children, Massachusetts General Hospital

#### WEDNESDAY, MARCH 17

\*9 00-10 00 a m Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon Joseph H Pratt Diagnostic Hospital

\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*2 00-3 00 p m Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater, Children's Hospital

\*Open to the medical profession

MARCH 5-31 Joseph H Pratt Diagnostic Hospital Medical Conference Program Page 343

MARCH 8 Boston City Hospital House Officers' Association Notice above

MARCH 9 Harvard Medical Society Page 210, issue of February 26  
MARCH 9 New England Society of Anesthesiologists Page 310 issue of February 26

MARCH 9 New York Tuberculosis and Health Association Page 136 issue of January 22

MARCH 11 Diagnosis and Treatment of Painless Jaundice Dr Chester M Jones Pentucket Association of Physicians 8 30 p m Haverhill

MARCH 11 Fiftieth Anniversary of Cornell University Medical College Page 136 issue of January 22

MARCH 12 and 13 American Association of Pathologists and Bacteriologists Page 204 issue of February 5

(Notices concluded on page xvi)

## NOTICES (Concluded from page 344)

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons American Industrial Hygiene Association American Conference of Governmental Industrial Hygienists American Association of Industrial Nurses Inc. and American Association of Industrial Dentists Hotel Statler Boston

APRIL 7, 9, 14 and 16 American Trudeau Society Page 240 Issue of February 12

APRIL 10 American Congress of Physical Medicine Page 344

APRIL 19-23 American College of Physicians Page xlii issue of July 31

APRIL 29-MAY 2 American Academy of Pediatrics Page 240 Issue of February 12

MAY 6. Suffolk Censors Meeting Page 344

MAY 6-8 American Association for the Study of Gynecology Page xlii issue of July 31

MAY 16-22 American Board of Obstetrics and Gynecology Inc. Page 344

MAY 16-23 International College of Surgeons Page 136, issue of January 22

MAY 17-20 American Urological Association Hotel Statler Boston

MAY 18-22 American Association on Mental Deficiency Copley Plaza Hotel Boston

MAY 20-25 American Board of Ophthalmology Page 170 issue of January 29

MAY 25-27 Massachusetts Medical Society Annual Meeting Hotel Statler Boston

JUNE 28-30 American Academy of Pediatrics 111 Schroeder Milwaukee Wisconsin

JULY 12-17 First International Poliocongress Conference Page 36 Issue of January 1

AUGUST 11-21 International Congress on Mental Health Page 344

SEPTEMBER 13-15 American Academy of Pediatrics Olympic Hotel Seattle Washington

SEPTEMBER 20-23 American Hospital Association Page 110 Issue of February 16

SEPTEMBER 29 Mississippi Valley Medical Association Page 170 Issue of January 29

OCTOBER 6-9 American Board of Ophthalmology Page 170 Issue of January 29

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chilton-Haddon Hall Hotel Atlantic City New Jersey

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

MARCH 9 Franklin County Hospital Greenfield  
MAY 11 Annual Meeting Hotel Walden Greenfield

## MIDDLESEX EAST

MARCH 24  
MAY 12 Annual Meeting  
Meeting will be held at the Bear Hill Golf Club Wakefield

## NORFOLK

MARCH 21 Harvard Night

## PLYMOUTH

MARCH 18 Goddard Hospital Brockton  
APRIL 15 State Farm Bridgewater  
MAY 10 Lakeville Sanatorium Lakeville

## SUFFOLK

MAY 6 Censors Meeting

## WORCESTER

MARCH 10 Memorial Hospital Worcester  
APRIL 14 Worcester Massena Hospital  
MAY 12 Annual Meeting

# MEDICAL BOOKS

of all  
Publishers

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## The Ophthalmological Study Council BASIC COURSE IN OPHTHALMOLOGY

Westbrook Junior College, Portland Maine June 10 to  
September 11 1948 All the basic subjects required by  
the American Board of Ophthalmology Laboratory  
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Council, 520 Commonwealth Avenue Boston 15 Mas-  
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## Old Way...

### CURING RICKETS in the CLEFT of an ASH TREE

FOR many centuries,—and apparently down to the present time, even in this country—ricketic children have been passed through a cleft ash tree to cure them of their rickets, and thenceforth a sympathetic relationship was supposed to exist between them and the tree.

Frazer\* states that the ordinary mode of effecting the cure is to split a young ash sapling longitudinally for a few feet and pass the child, naked, either three times or three times three through the fissure at sunrise. In the West of England, it is said the passage must be "against the sun." As soon as the ceremony is performed, the tree is bound tightly up and the fissure plastered over with mud or clay. The belief is that just as the cleft in the tree will be healed, so the child's body will be healed, but that if the rift in the tree remains open, the deformity in the child will remain, too, and if the tree were to die, the death of the child would surely follow.

\*Frazer J. G.: *The Golden Bough*, vol. 1. New York, Macmillan & Co., 1922.



It is ironical that the practice of attempting to cure rickets by holding the child in the cleft of an ash tree was associated with the rising of the sun, the light of which we now know is in itself one of Nature's specifics.

## New Way...

### Preventing and Curing Rickets with OLEUM PERCOMORPHUM

NOWADAYS, the physician has at his command, Mead's Oleum Percomorphum, a Council-Accepted vitamin D product which actually prevents and cures rickets, when given in proper dosage.

Like other specifics for other diseases, larger dosage may be required for extreme cases. It is safe to say that when used in the indicated dosage, Mead's Oleum Percomorphum is a specific in almost all cases of rickets, regardless of

degree and duration. Mead's Oleum Percomorphum because of its high vitamins A and D content is also useful in deficiency conditions such as tetany, osteomalacia and xerophthalmia.

\* \* \*

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## TOTAL PANCREATECTOMY\*

EUGENE A. GASTON, M.D.†

FRAMINGHAM, MASSACHUSETTS

AN INCREASING interest in surgery of the pancreas has been manifested since the demonstration by Whipple,<sup>1</sup> in 1935, of the practicability of partial pancreatectomy for the relief of cancer arising in or about the head of the pancreas. A natural outgrowth of this interest is recent efforts aimed at the feasibility of total pancreatectomy not only for the elimination of more extensive cancers but also for the relief of certain types of benign pancreatic disease. To date 16 cases of total pancreatectomy have been reported in the literature. Because the physiologic changes incident to total pancreatectomy in man are as yet imperfectly understood, it is important that observations made during and subsequent to this type of surgery be reported, so that the accumulated experience may eventually permit evaluation of its proper place in treatment. The purpose of this communication is to review the pertinent literature and to present a case of carcinoma involving the entire pancreas recently treated at the Framingham Union Hospital. In addition to resection of all of the pancreas the following structures were removed at operation: the spleen, the pyloric antrum of the stomach, all of the duodenum, 15 cm. of jejunum, the lower half of the common bile duct and the right half of the transverse colon.

### CASE REPORT

A 70-year-old man was admitted to the hospital on May 23, 1947, complaining of upper abdominal pain of 4 months' duration. Two years before admission the patient had begun to limit his diet without medical advice, because of obesity. This was followed by gradual loss of weight, which had become somewhat accelerated during the last 4 months and which totaled 32 pounds. One year before admission the gradual onset of constipation was noted. This became gradually worse and during the last 6 months required a daily enema. Occasional tarry stools had been noted but there had been no gross blood. Four months before admission he applied strong pressure to the lower sternal and epigastric regions in using a heavy electric drill which "shook him up" considerably. Four hours later he noted the sudden onset of epigastric pain which since then had been more or less constantly present and which was described as a gnawing

sensation radiating to the midline of the lower dorsal region. The pain was aggravated by food was partially relieved by sitting or standing and by pressure applied to the epigastrium and was not affected by alkalis. One month before admission an x-ray diagnosis of duodenal ulcer was made at another institution and the patient was placed on a six meal bland diet without relief. Two weeks before admission increasing pallor and weakness associated with some dyspnea on exertion was noted. At about that time he also noted slight itching of the skin. The urine was dark, although the stools were normal in color or occasionally tarry black. On the day of admission while driving his car he suddenly became disoriented and somewhat disoriented. This condition persisted for about 2 hours after which his mental state gradually returned to normal. The patient was known to have had hypertension for about 6 months but when he was seen by a physician after this episode, the blood pressure was found to be 125/70.

A review of the systems indicated no symptoms except a history of several years' duration. The past and family histories were noncontributory.

Physical examination revealed an elderly, thin, pale man with no distress. There was a slight icteric tint to the skin and sclerae. The head, neck, and chest were normal. The heart was not enlarged, rhythm was regular and there were no murmurs. The lungs were clear. The abdomen was soft and readily examined. There was slight tenderness in the midline between the xiphoid and umbilicus but no muscle spasm or rebound tenderness. No masses were palpable. The genitalia and extremities were normal; the prostate was not palpably enlarged, and no masses were felt by rectum.

The temperature, pulse and respirations were normal. The blood pressure was 140/70.

The specific gravity of the urine varied from 1.003 to 1.016. Bile was present in each of seven specimens, but there was no albumin or sugar. Except for an occasional white cell the sediment was normal. No urobilinogen was found in either of two specimens tested. Examination of the blood disclosed a red-cell count of 2,050,000 with a hemoglobin of 6.5 gm. per 100 cc. and a white-cell count of 5600. The blood smear was normal except for moderate hypochromia. The blood sugar was 141 mg. per 100 cc. on the day after admission and 95 mg. several days later. The nonprotein nitrogen was 56 mg. per 100 cc. on admission falling to 37 mg. on the day before operation. The total protein was reported as 6.0 gm. per 100 cc. with an albumin globulin ratio of 4:1. After the transfusion of 4500 cc. of blood over the following 12 days, the total protein was 8.0 gm. per 100 cc., with an albumin globulin ratio of 1:1. The prothrombin time was within normal limits and the initial icteric index was 16. Two attempts to determine the total blood volume by the use of the dye T 1824 were frustrated by the presence of jaundice which made it impossible to obtain satisfactory colorimetric readings. The presence of the blue dye in the blood serum made it impossible to secure satisfactory readings of the icteric index subsequent to admission although clinically the patient became progressively more jaundiced. Each of nine stool specimens was strongly positive for occult blood and one was reported to be negative. The stools were brown during the early part

\*From the Surgical Service, Framingham Union Hospital and the Department of Surgery, Boston University School of Medicine.  
†This study was aided by the Research and Publication Fund of the Framingham Union Hospital.

†Assistant Professor of Surgery, Boston University School of Medicine, Framingham Union Hospital.

of the hospital stay but became clay colored thereafter. Gastric analysis revealed no free hydrochloric acid.

Electrocardiographic tracings disclosed left-axis deviation but were otherwise normal. X-ray examination of the chest showed the lungs to be clear, the heart was not enlarged. A barium enema demonstrated that the colon was normal. The esophagus and stomach were normal on gastrointestinal x-ray study. There was definite widening of the duodenal loop, indicating enlargement of the head of the pancreas. The duodenal mucosa revealed no evidence of ulceration, a cholecystogram was not done because of the presence of jaundice.

The patient was studied for 12 days preceding operation, during which the temperature, pulse and respirations were within normal limits. The blood pressure gradually rose

bile duct was freed from the portal vein and hepatic artery and divided in its supraduodenal portion, the portal vein was accidentally lacerated but was satisfactorily repaired. The neck of the pancreas was easily freed from the underlying portal and superior mesenteric veins. The uncinate process was small and not adherent to the superior mesenteric vessels and was easily dissected free. At this point it was found that the blood supply to the transverse colon was anomalous and that the vessels supplying the right half extended through the neoplastic mass in the head of the pancreas. After the duodenum had been divided at the ligament of Treitz and mobilized to the right under the superior mesenteric vessels, the anomalous vessels to the right half of the transverse colon were divided, completing the mobilization of the duodenum and the head of the

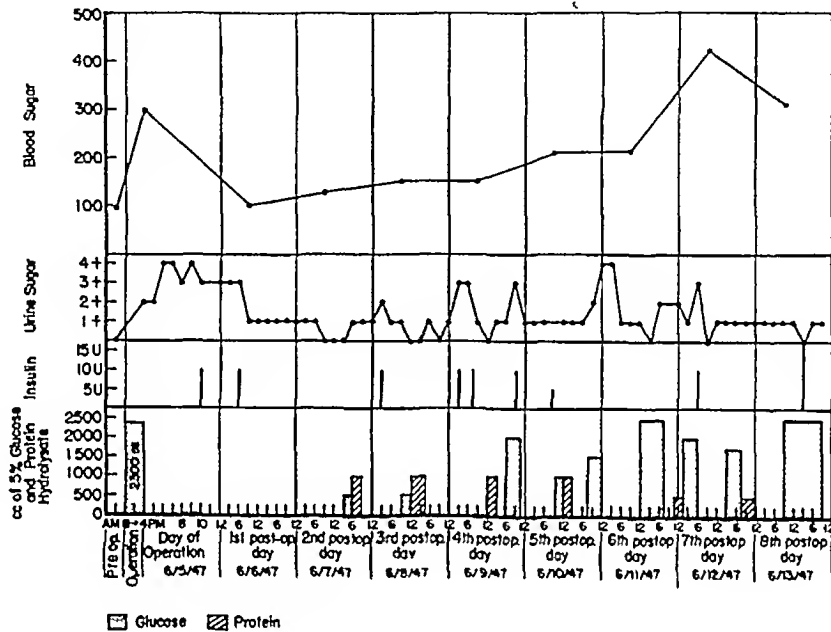


FIGURE 1 The Diabetic State after Total Pancreatectomy

from 140/70 on admission to 200/90 on the day before operation. The icterus became progressively deeper, the urine continued to show the presence of bile, and the stools changed from brown to clay colored. Food and fluids were well tolerated, and the diet was supplemented by daily intramuscular injections of crude liver extract, vitamin C and vitamin K. The prothrombin time did not vary significantly from the normal. Although the patient had Type A, Rh— blood, a total of 4500 cc of whole blood was given without reaction, and at the end of the preoperative period he was considered to be a fair operative risk.

Operation was performed June 5 under continuous spinal anesthesia supplemented with intravenous Pentothal Sodium and small amounts of ether. A long, right-rectus-muscle-splitting incision was made and later enlarged by a connecting transverse incision extending across the upper abdomen to the left costal margin. The entire head, neck, body and tail of the pancreas were indurated, apparently owing to diffuse invasion by a neoplastic process that had not grossly invaded the surrounding structures. The liver was dark from jaundice and slightly enlarged but contained no metastatic nodules. The gall bladder was thin walled and markedly distended with thick, black bile, which was aspirated to facilitate exposure. The common bile duct was about 1.5 cm. in diameter. After the gastroduodenal omentum had been divided a biopsy of the middle of the body of the pancreas was submitted to Dr. C. G. Tedeschi for frozen-section examination and was reported as showing the presence of carcinoma. Since the entire pancreas was obviously involved a total pancreatectomy was decided upon.

The stomach was divided about 7.5 cm. proximal to the pyloric sphincter, and the duodenum mobilized. The gastroduodenal vessels were identified and divided. The common

pancreas. Exposure for the mobilization of the body and tail of the pancreas was then greatly facilitated by division of the pancreas at its neck and removal of the mobilized pyloric antrum, duodenum and head of the pancreas. It was then evident that the splenic vessels were surrounded by neoplastic tissue. The spleen was therefore mobilized by division of the short gastric and left gastroepiploic vessels. The splenic artery and vein were divided close to their points of origin, and the body and tail of the pancreas and the spleen were removed.

About 15 cm. of jejunum distal to the ligament of Treitz had been resected to assure an adequate blood supply, the end of the jejunum was closed. A loop of proximal jejunum was brought through a rent in the transverse mesocolon, and end-to-side anastomoses were completed between the jejunum and the stumps of the stomach and common bile duct, the latter about 10 cm. distal to the former. After these had been completed it was evident that the blood supply to the right half of the transverse colon was inadequate. The hepatic flexure of the colon was mobilized, and the right half of the transverse colon delivered through the middle of the wound and amputated over clamps to form a double-barreled colostomy. A catheter was sutured into the gall bladder and brought out through a stab wound in the right flank. A rubber tissue drain was placed in the bed of the pancreas and brought out through a second stab wound in the right flank. The wound was closed around the two loops of the transverse colostomy.

During the operation, which required 6½ hours, the patient received 2300 cc of 5 per cent glucose in distilled water, 1500 cc of whole blood and 300 cc of plasma. The anesthesia required 455 mg of procaine, 52 mg of pontocaine, 1.5 gm of Pentothal Sodium and 28.3 gm of ether. The patient

withstood the operative procedure remarkably well but when the operation had been completed the pulse rate was 130 and the blood pressure 90/55.

The immediate postoperative response to continued intravenous therapy was very satisfactory; the pulse rate and blood pressure rapidly approximating preoperative levels.

careful attention to the diabetic state since the entire pancreas had been removed.

The first 4 days of the postoperative course were remarkably smooth. The temperature and pulse curves progressively fell toward normal; peristalsis returned on the fourth day and the patient was mentally alert and physically active.

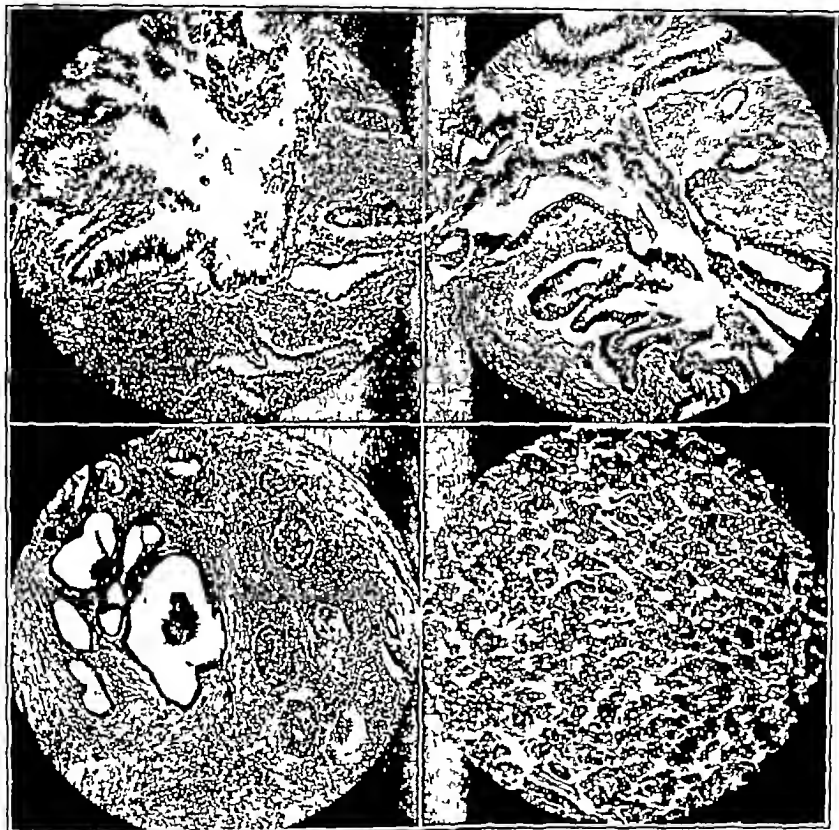


FIGURE 3

A shows specimen from ulcerated area in second portion of duodenum illustrating normal duodenal glands and closely adjacent adenocarcinoma. B demonstrates section from head of pancreas showing extensive malignant infiltration. C illustrates portion from tail of pancreas showing dilated ducts, one of which contain a clump of malignant cells (note enlargement of pancreatic islets). D demonstrates liver showing some but not marked fatty replacement.

Postoperative treatment consisted in decompression of the gastrointestinal tract by means of suction applied to a Levine tube which was continued for 4 days; the administration of adequate intravenous fluids including glucose, physiologic saline solution, protein hydrolysate, plasma and whole blood (a total of 4000 cc. of blood during and after operation); penicillin and streptomycin in large doses; and

The proximal loop of the colostomy was opened at that time and the wound appeared to be clean. On the evening of the 11th day the temperature rose to 101 F. and on the following day sepsis around the distal loop of the colostomy was discovered. The wound was opened and extensive undermining by pus was discovered between the intact peritoneum and the overlying muscle. The entire septic area was widely



opened, cultured and packed with gauze, which was kept saturated with a mixture of urethane and penicillin.<sup>2</sup> At the same time the dose of penicillin, which until then had been 100,000 units every 3 hours, was increased to 500,000 units every 3 hours, to which 500 mg of streptomycin was added. In spite of the most vigorous treatment the temperature and pulse continued to rise, and the patient became disoriented and finally comatose and died on the 8th postoperative day. The urinary output was maintained between 1200 and 2400 cc daily, and yet the nonprotein nitrogen remained elevated to between 50 and 60 mg per 100 cc until the day before death, when it rose to 70, reaching 107 mg per 100 cc on the day of death. Throughout the postoperative course the serum chloride remained within normal limits, varying from 550 to 620 mg per 100 cc. The cholecystostomy drained relatively small amounts of bile, the maximum being 320 cc on the 2nd postoperative day. The icteric index fluctuated between 49 and 59 until the day of death, when it reached 75.

The postoperative diabetic state was followed closely. Fresh urine specimens were tested hourly for sugar and diacetic acid for 3 days and every 3 hours thereafter. The blood sugar level and carbon dioxide combining power were determined daily. At no time did the urine show diacetic acid, and the carbon dioxide combining power was consistently within normal limits, ranging from 53 to 69 vol per cent. Figure 1 shows graphically the relation of the levels of sugar in the blood and urine to the administration of insulin, intravenous glucose and protein hydrolysate. As in other cases of total pancreatectomy this patient proved to be relatively mildly diabetic. Because of the increased sensitivity to insulin reported after total pancreatectomy, efforts in the treatment of the diabetes were directed to the prevention of acidosis rather than to the maintenance of normal blood sugar levels.

It will be noted from Figure 1 that in spite of the administration of 115 gm of intravenous glucose during operation only 20 units of insulin was given during the next 17 hours. At the end of that period the blood sugar level was 101 mg per 100 cc. During the next 30 hours during which neither glucose nor insulin was administered, the urinary excretion of sugar fell to zero, and the blood sugar remained within normal limits. The largest amount of insulin required during any 24-hour period was during the 4th postoperative day, when a total of 30 units was given. From the 5th to the 8th postoperative day there was a progressive rise in blood sugar levels that was probably related not only to the increased administration of glucose and protein hydrolysate but also to the onset of sepsis.

Because of the short period of survival following the operation, there was no opportunity to make observations on the effects of elimination of other pancreatic secretions. However, on the 5th day after operation the serum lipase was reported as 0.1 cc N/20 NaOH (normal, 0.1 to 1.0 cc).

The surgical specimen consisted of the distal 6 cm of stomach, all of the duodenum and an additional 10 cm of upper jejunum, all of the pancreas and spleen and 24 cm of transverse colon. The resected stomach and jejunum showed no gross or microscopical abnormalities. The transverse colon showed gross and microscopical evidence of infarction (due to ligation of its blood supply at operation) with widespread hemorrhagic changes and vascular congestion affecting all coats, the mucosa most severely. The entire head, body and tail of the pancreas were indurated and of variegated appearance due to alternating yellowish-pink, lobulated areas still preserving the characteristics of pancreatic tissue, and of grayish-pink translucent areas suggesting neoplastic tissue. An area of indurated ulceration 2 cm in diameter was found on the lesser curvature of the second portion of the duodenum. On microscopical examination this area of the duodenum, as well as the entire pancreas, showed evidence of a neoplastic process characterized by atypical glandular structures and by anaplastic cells disposed in cords or in rudimentary alveoli imbedded in fibrous connective tissue. The pancreatic islands were well preserved and, particularly in the region of the tail, appeared to be larger than normal (Fig 2A, B and C). The spleen showed no gross or microscopical abnormalities.

Autopsy was performed 1¼ hours post mortem. About 200 cc of purulent, blood-tinged fluid was found encysted between the lesser curvature of the stomach and the liver.

From this fluid were cultured *Escherichia coli*, *Proteus vulgaris* and *Pseudomonas aeruginosa*. A second area of encysted fluid, containing about 600 cc, was observed in the bed of the removed spleen. This fluid was watery and blood tinged and was not infected. The remainder of the abdominal cavity was clean. The gastrojejunal and cholodochojejunal anastomoses were well healed and patent.

The liver was somewhat enlarged, weighing 1500 gm, and except for moderate jaundice disclosed no gross abnormalities. On microscopical examination the liver cells in the center of the lobules showed regressive changes ranging from cloudy swelling to fatty degeneration, which, however, was moderate and did not compare with the extensive changes noted in a depancreatized dog (Fig 2D). Bile casts were noted as well as a patchy distribution of inflammatory cells, chiefly lymphocytes and histiocytes. The Kupffer cells stood out conspicuously, and many were seen to contain blocks and granules of yellowish-brown pigment.

No gross evidence of metastasis was found. However, on microscopical examination small clumps of neoplastic cells similar to those found in the pancreas were found in both the cortex and the medulla of the left adrenal gland. Other important autopsy findings were generalized atherosclerosis, hypertrophy and dilatation of the left ventricle, myocardial fibrosis, left hydrothorax, pulmonary congestion and edema, purulent bronchitis and bronchiolitis and renal arteriosclerosis.

## SURGICAL RESULTS

The first authenticated case of total pancreatectomy was reported by Rockey<sup>3</sup> in 1943. This operation was performed for carcinoma arising in the body of the pancreas. The patient survived fifteen days, succumbing to bile peritonitis due to a "blow out" of the ligated end of the common bile duct. Of historical interest only are 2 cases culled from the literature by Sauve<sup>4</sup> in both of which nearly total pancreatectomies were done. The first of these was credited to Billroth by Mayo-Robson in 1901, the operation having been done in 1884. Since this case was never fully reported the exact extent of the operation and the end result are unknown. The second case was reported by Franke in 1900. This operation was also done for cancer of the pancreas, but the duodenum was not removed and a mass of pancreatic tissue "the size of a hazel nut" was left behind. Only transient glycosuria developed rather than severe diabetes as might have been expected from recent experimental findings discussed below. The patient survived five and a half months, dying from recurrent cancer.

The 16 reported cases of total pancreatectomy, together with the case presented above, are described in Table 1. Eleven operations were done for cancer, and only 3 patients survived the immediate postoperative period—an operative mortality of 73 per cent. Of the 3 who survived operation, 1 died in three and a half months of carcinomatosis, the second was living without known recurrence four months after operation, and the third was living with probable recurrence fifteen months after operation. It appears that the efficacy of total pancreatectomy for the cure of malignant tumors remains to be demonstrated. Of the 6 patients with benign disease, 4 were operated upon for pancreaticolithiasis, with an operative mortality of 50 per cent. Of the 2 survivors, 1 died of an in-

sulin reaction at the end of two and a half months, and the other was alive and free of abdominal pain a year after operation, but institutionalized because of pulmonary tuberculosis. Pancreatectomy was performed in the remaining 2 cases because of hyperinsulinism due to islet-cell adenomas that were small and so buried in the head of the pancreas that they could not be demonstrated at operation. At the time of the reports both patients were living and well, 1 thirty-seven months<sup>8</sup> and the other eight months<sup>8</sup> after operation. In the 17 cases of total pancreatectomy for all causes, 7 patients survived operation and 10 died, an operative mortality of 59 per cent.

Although, to date, the surgical mortality and the end results of total pancreatectomy leave much to be desired, it is probable that with increasing experience cure rates may be elevated and mortality figures reduced to acceptable limits. This has certainly been the experience with many operative procedures — for instance, with total gastrectomy — during recent years.

#### PHYSIOLOGIC CHANGES

##### *The Diabetic State*

The diabetic state that follows total pancreatectomy in man appears to be relatively mild. In the first case of total pancreatectomy, reported by Rockey,<sup>3</sup> the patient was given 67 units of insulin to cover intravenous glucose on the day of operation and 93 units on the following day. These doses were followed by severe and prolonged insulin reactions. Eventually, the daily insulin requirement was found to be only 27 units. Since then many authors have noted the relatively low insulin dosage required during the immediate postoperative period. To date only 7 patients have survived for longer periods, and these cases are listed in Table 2 along with the daily food intake and insulin requirement. In these cases the average daily insulin requirement was about 42 units, with a carbohydrate intake that averaged 289 gm.

Of particular interest in this connection are the cases reported by Brunschwig and his associates<sup>10</sup> and by Dixon et al.<sup>11</sup> In both these cases diabetes was present before total pancreatectomy was done. One patient, a fifty-three-year-old man, had had known diabetes for nine months preceding operation.<sup>10</sup> During the preoperative period, during which his weight was 72 kg (158 lb), the diabetes was controlled by 40 to 65 units of insulin per day on a diet of 398 gm of carbohydrate, 200 gm of protein and 12 gm of fat (glucose equivalent of 511 gm). Two months after operation the insulin requirement was reduced to about 40 units per day on a diet of 401 gm of carbohydrate, 102 gm of protein and 11 gm of fat (glucose equivalent of 459 gm). At that time the body weight had fallen to 56 kg (123 lb). The authors point out that the apparent reduction in the demand for insulin may have been due to two factors: the lower glucose value

of the postoperative diet and the loss of 16 kg of weight. The striking fact, however, is not that the insulin requirement was not more greatly reduced but that it was not greatly augmented by total pancreatectomy. From these observations the authors conclude that the insulin production of the normal pancreas is in the range of 30 to 50 units per day and that in diabetic patients requiring more than this amount, an extrinsular factor must be contributing to the diabetic syndrome.

The patient of Dixon et al.<sup>11</sup> was a fifty-year-old man who had known diabetes of nineteen months' duration before total pancreatectomy. During the preoperative period the diabetes was controlled with 24 units of protamine-zinc insulin daily. Seven months after operation 40 units of protamine-zinc insulin daily was required.

These and other observations have led to speculation regarding whether clinical diabetes, which often requires doses of insulin far in excess of those reported after total pancreatectomy, is entirely due to degeneration of insular tissue. Goldner and Clark,<sup>9</sup> after observations in 2 cases of total pancreatectomy with shorter survival periods, state that "The question must be raised whether in the causation of diabetes not only lack of insulin but also an insulin-inhibiting mechanism may play a role." Experimental evidence pointing in this direction was presented by Dragstedt, Allen and Smith,<sup>12</sup> who found the insulin requirement of partially depancreatized dogs to exceed that required after total pancreatectomy. Sprague,<sup>6</sup> however, believes that even if the insulin requirement of the depancreatized human being proves to be consistently less than that of many patients with severe diabetes, the conclusion that spontaneous diabetes and surgical diabetes are basically different is not justified. He points out that the insulin requirement in spontaneous diabetes is subject to a wide variety of influences, one of the most important of which is cachexia from any cause, which not only reduces the requirement for insulin but also may even lead to hypoglycemic coma without the administration of insulin. The poor nutritional state of patients after total pancreatectomy may well tend to ameliorate the diabetes and lower the insulin requirement. Furthermore, nothing is known of the effect of total pancreatectomy on the glycogenic and glycolytic functions of the liver, alterations of which might profoundly affect the diabetic state.

A state of apparently increased sensitivity to insulin has been present during the early postoperative period in nearly all reported cases, and Clagett's<sup>13</sup> patient died of an insulin reaction two and a half months after operation. These observations are of great importance in the management of patients after total pancreatectomy. It is evident that treatment during this period should be directed more toward the prevention of ketosis than to the control of the blood sugar levels. To date no case of

insulin resistance has been reported after total pancreatectomy

Evidence that ketogenesis follows total pancreatectomy in man is scanty but indicates a similar-

withdrawn Glycosuria and ketosis promptly appeared, and death occurred in typical diabetic coma six days later Dixon's<sup>6</sup> case was studied during two periods of insulin deprivation of eighty-nine

TABLE 1 Cases of Total Pancreatectomy Reported in the Literature

CASE No	AUTHOR	SEX	AGE	DIAGNOSIS	OTHER OPERATIVE PROCEDURES	SURVIVAL	CAUSE OF DEATH
1	Rockey <sup>8</sup>	M	51	Adenocarcinoma arising in body of pancreas	Partial (distal half) gastrectomy, total duodenectomy	15 days	Bile peritonitis due to "blow out" of ligated common bile duct
2	Priestly et al. <sup>8</sup> Vaugh et al. <sup>8</sup>	F	49	Hyperinsulinism due to islet-cell adenoma	Partial (distal third) gastrectomy, partial (first and second portions) duodenectomy	Patient living and well 37 mo after operation	—
3	Brunschwig <sup>7</sup> (Case H H 302199)	M	67	Carcinoma of entire pancreas	Total duodenectomy, splenectomy	3 days	Massive bilateral pulmonary consolidation
4	Brunschwig <sup>7</sup> (Case N R. 309791)	M	29	Diffuse carcinoma of pancreas	Total duodenectomy, splenectomy	9 days	Exhaustion
5	McClure <sup>8</sup> (Case of Fallis)	M	46	Primary carcinoma of pancreas	Total duodenectomy, splenectomy	Patient living and well 4 mo after operation	—
6	Goldner and Clark <sup>8</sup> (Case of Brunschwig)	Not stated	Not stated	Carcinoma of bile duct invading pancreas	Not stated	11 days	Gastric hemorrhage, early peritonitis
7	Goldner and Clark <sup>8</sup> (Case of Clark)	M	45	Papillary carcinoma of common bile duct with invasion into head of pancreas chronic pancreatitis	Partial duodenectomy, pylorotomy, splenectomy	10 days	Hepatorenal failure and uremia
8	Brunschwig et al. <sup>10</sup> Ricketts et al. <sup>11</sup> Ricketts et al. <sup>12</sup> (Case F W 328218)	M	53	Carcinoma arising in body of pancreas with extension to stomach and left adrenal gland, metastasis to lymph nodes	Total gastrectomy, total duodenectomy, splenectomy, left adrenalectomy, omentectomy	3½ mo	Carcinomatosis and diabetic coma due to insulin withdrawal
9	Whipple <sup>13</sup>	F	26	Chronic pancreatitis, pancreaticolithiasis	Pylorotomy, total duodenectomy	Patient alive, with pulmonary tuberculosis 1 yr after operation	—
10	Whipple <sup>13</sup>	F	46	Fibrosis of pancreas, pancreaticolithiasis	Pylorotomy, total duodenectomy, splenectomy	7 days	Shock and pulmonary edema
11	Zininger <sup>14</sup>	M	39	Chronic pancreatitis, pancreaticolithiasis	Not stated	30 hr	Not stated
12	Brunschwig <sup>15</sup>	Not stated	Not stated	Carcinoma of pancreas	Not stated	14 days	Not stated
13	Vaugh et al. <sup>8</sup>	F	36	Hyperinsulinism due to islet-cell adenoma	Pylorotomy, partial duodenectomy	Patient living and well 8 mo after operation	—
14	Dixon <sup>16</sup>	M	50	Carcinoma arising in head and involving half of pancreas remainder atrophic	Partial gastrectomy (distal half), total duodenectomy, splenectomy	Patient living with recurrent cancer 14 mo after operation	—
15	Clagett <sup>17</sup>	F	37	Chronic pancreatitis, diffuse calcification of pancreas multiple pancreatic calculi	Partial gastrectomy, partial duodenectomy, splenectomy	2½ mo	Insulin reaction
16	Brunschwig <sup>18</sup> (Case 348369)	Not stated	Not stated	Sarcoma — origin not stated	Subtotal (seven eighths) gastrectomy, total duodenectomy, splenectomy, transverse colectomy	19 days	Peritonitis due to leakage of gastrojejunostomy anastomosis
17	Gaston	M	70	Adenocarcinoma probably arising in papilla of Vater and invading entire pancreas	Pylorotomy, total duodenectomy, splenectomy, transverse colectomy	8 days	Peritonitis secondary to wound sepsis uremia

ity to that produced in untreated spontaneous diabetes and in depancreatized dogs. The patient of Brunschwig<sup>10, 11</sup> developed recurrent cancer, and three and a half months after operation, insulin was

hours each, the first beginning on the sixty-sixth and the second on the two hundred and forty-fifth postoperative day. During the first interval the diet contained 440 gm of carbohydrate daily, and

whereas the blood sugar level rose to 813 mg per 100 cc, the carbon dioxide combining power remained within normal limits and the urine showed a faint trace of acetone only during the last eight

chloride by mouth. In spite of a large urinary output the blood urea rose to 57 mg per 100 cc. During the second interval of insulin privation the diet contained only 120 gm of carbohydrate, and a salt

TABLE 1 (Continued)

CASE No.	DIET	DAILY INSULIN	EXTERNAL PANCREATIC SECRETION STUDIES	PLASMA LIPIDS	LIVER AND LIVER FUNCTION STUDIES	REMARKS
1	—	27 units (frequent insulin shock 1 early post-operative period)	—	—	Liver normal at autopsy	Slightly less than 1 gm. of pancreatic tissue found at autopsy
2	Carbohydrate 243 gm.; protein 94 gm.; fat, 70 gm.	30 units	Recovered in feces 35-70 per cent. + coated fat, 5-5 per cent of ingested nitrogen; recovered in urine and feces 21-34 per cent. + coated calori	Normal 37 mo. after operation	Bromsulphalein retention normal 30 mo. after operation	—
3	—	—	—	—	—	—
4	—	Less than anticipated	—	—	—	—
5	—	26 units of protamine zinc insulin daily 8 units of regular insulin twice weekly	—	—	—	—
6	150 to 200 gm. of glucose parenterally	50 units	—	—	—	—
7	150 to 200 gm. of glucose parenterally	30 to 40 units	—	—	—	Neoplasm extended into wall of portal vein and around celiac axis preventing complete eradication
8	Carbohydrate, 401 gm; protein 102 gm.; fat, 11 gm.	30 units of protamine zinc insulin 10 units of regular insulin (frequent hypoglycemic reactions)	—	Slowly declined but never abnormal	Liver fatty at autopsy probably owing to death in diabetic coma	Patient diabetic before operation requiring more insulin than after operation; pre-operative diabetes spot tanes and not due to tumor
9	Carbohydrate, 300 gm.; protein 70 gm.; fat, 75 gm.	30 to 80 units	—	—	—	—
10	—	50 to 90 units (failed to control glycosuria)	—	—	—	Autopsy revealed localized bile peritonitis and thrombosis of large branch of portal vein
11	—	30 to 50 units	—	—	—	—
12	—	Not stated	—	—	—	—
13	Carbohydrate 267 gm.; protein 125 gm.; fat, 103 gm.	26 units of regular insulin 6 units of protamine-zinc insulin	—	Normal 70 days postoperatively slightly below normal 123 days postoperatively; probably due to jaundice	—	—
14	Carbohydrate, 272 gm.; protein 107 gm.; fat 100 gm.	30 units of regular insulin 10 units of protamine-zinc insulin	Nitrogen loss in stool 4 to 8 gm. (normal less than 1.5 gm.); fat loss in stools 36 to 48 gm. (normal 6 to 7 gm.)	Increase of 100 per cent 8 mo. after operation	Bromsulphalein retention normal 8 mo. after operation	Patient diabetic 19 mo. before operation requiring 30 units of insulin daily
15	Carbohydrate 250 gm.; protein 75 gm.; fat, 101 gm.	30 units of regular insulin 8 units of protamine zinc insulin	—	Normal 1 mo. after operation	Bromsulphalein retention normal 1 mo. after operation	Prolonged drainage of common bile duct did not relieve symptoms before pancreasectomy
16	—	Diabetes did not appear unusually severe or difficult to control	—	—	—	—
17	50 to 150 gm. of glucose daily parenterally	10 to 30 units regular insulin daily	—	—	Liver normal at autopsy	—

hours. During this interval the plasma chloride level fell to 507 mg per 100 cc, and the patient complained of abdominal cramps, which were relieved by the administration of 3 gm of sodium

mixture was given to prevent the unpleasant symptoms associated with hypochloremia. On the lower carbohydrate intake liver glycogen was depleted, and conditions more favorable to the development

of ketosis were provided. During the second period ketonemia was marked.

At this time no information is available regarding whether totally depancreatized human beings will eventually develop the degenerative changes associated with prolonged spontaneous diabetes, although atheromatosis and arteriosclerosis have been reported in depancreatized dogs.<sup>21</sup>

### Liver Changes

It has long been known that totally depancreatized dogs maintained on adequate diets and insulin cannot be kept in a state of health for long periods. After four to six weeks on such a regime the animals begin to show a decrease in glucose excretion, increased insulin sensitivity, hypolipemia and a loss of appetite with cachexia. The general condition progressively deteriorates and ends in death, usually within a few months. At autopsy a

in lecithin, it probably represents a true internal secretion of the pancreas.

Associated with the fatty changes in the liver is a gradual reduction in plasma lipoids that begins four or five weeks after pancreatectomy in dogs and falls to about 50 per cent of the normal level by the twentieth week after operation.<sup>32</sup>

Few observations are available concerning the plasma lipoids and liver function in totally depancreatized human beings. Plasma lipid studies have been reported in 5 of the 17 cases in the literature (Cases 2, 8, 13, 14 and 15 in Table 1). Of the cases in Table 1, Cases 2 and 15 showed normal plasma lipoids thirty-seven months and one month, respectively, after operation. In Case 8 the values of plasma lipoids slowly declined during the three and a half months of survival but were never abnormal. In Case 13 the plasma lipoids were normal seventy days after operation but were slightly below normal

TABLE 2 *Insulin Requirement in Patients Surviving Immediate Postoperative Period*

AUTHOR	AGE OF PATIENT	SEX	TIME OF SURVIVAL	DAILY FOOD INTAKE			DAILY INSULIN REQUIREMENT
				CARBO-HYDRATE	PROTEIN	FAT	
	yr		mo	gm	gm	gm	units
Priestly et al. <sup>1</sup>	49	F	37	243	94	70	30
McClure <sup>2</sup>	46	M	4				26-34
Brunschwig <sup>3</sup>	53	M	3½	401	102	11	40
Whipple <sup>13</sup>	26	F	12	300	70	75	30-80
Waugh et al. <sup>4</sup>	36	F	8	267	125	103	32
Dixon <sup>16</sup>	50	M	14	272	107	100	40
Clagett <sup>17</sup>	37	F	2½	250	75	101	38

majority of the animals, but not all, display a remarkable accumulation of fat in the liver, and the resulting impairment of liver function can be accurately estimated before death by the degree of retention of bromsulfalein.<sup>22</sup> Fisher<sup>23</sup> and Allan et al.<sup>24</sup> showed in 1924 that the addition of raw pancreas to the diet effectively prevented the changes in the liver and that the animals could be maintained in a state of health for long periods. Lecithin<sup>25, 26</sup> and later choline<sup>27, 28</sup> were found to prevent the deposition of fat in the liver when added to the diet in adequate quantities and also to cause the liver to return to normal after the condition had developed. More recently methionine has been shown to possess the same properties of prevention and cure.<sup>6, 29</sup>

In addition to the substances listed above, Dragstedt<sup>21, 30, 31</sup> has identified what he believes to be a second internal secretion of the pancreas, probably formed in the alpha cells, which has remarkable properties for preventing or curing the liver changes resulting from total pancreatectomy in dogs. This substance, which he terms "Lipocaic," is not present in the external secretion of the pancreas and has been prepared free of lecithin and practically free of choline. Since it has been found only in extracts of pancreas and not in extracts of other organs rich

on the hundred and twenty-third day. At the later examination the patient was jaundiced, and this fact may have played a part in lowering the values. In Case 14 a 100 per cent increase in plasma lipoids was found eight months after operation. The explanation of this is not clear, since at the same time the bromsulfalein retention was normal and exactly the opposite occurs after pancreatectomy in dogs.

The condition of the liver at autopsy has been described in 3 cases (Cases 1, 8 and 17 in Table 1). In 2 of these it was found to be normal fifteen days and eight days, respectively, after operation. In the other case the liver was described as fatty three and a half months after operation, but the cause of death was diabetic coma due to insulin withdrawal, which may have been responsible for the findings.

Bromsulfalein liver-function studies have been reported in 3 cases (Cases 2, 14 and 15 in Table 1) and were normal in all thirty-seven months, eight months and one month, respectively, after operation.

Although material concerning the effects of total pancreatectomy on the liver in man is scanty, it is evident from the discussion presented above that the gross fatty changes noted in depancreatized dogs have not been observed either clinically or at

autopsy. However, changes similar to those seen in the dog and responding to the administration of lipocain have been observed in spontaneous diabetes<sup>22</sup> and after destruction of the pancreas from repeated attacks of acute pancreatitis.<sup>20</sup> From these observations it is unlikely that the failure to observe in man the liver changes noted in the dog is due to a species immunity, although this factor must be considered, since it is well known that there is great variation in the severity of the diabetes and in the ability to form ketone bodies among different species of animals after depancreatization. It is more probable that the presence of choline and other lipotropic substances in the diet of man is sufficient to protect the liver.

### *Digestion and Absorption*

Experiences after ligation of the pancreatic ducts incident to partial pancreatectomy have led to conflicting reports on the effects of exclusion of the external secretion of the pancreas from the gastrointestinal tract.<sup>31-33</sup> Some patients develop bulky, frothy, foul-smelling stools, which contain large percentages of the ingested fat and nitrogen, whereas others remain relatively unaffected. Similar though less extensive loss of fat and nitrogen has been demonstrated after partial gastrectomy done for the relief of duodenal ulcer.<sup>37, 38</sup> Experimental work on dogs after complete pancreatectomy, the production of a complete pancreatic fistula or evulsion of the pancreatic ducts showed a marked loss of fat and carbohydrate in the feces.<sup>39, 40</sup> An increased excretion of fecal nitrogen was related to the increased bulk of the feces, which was less when diets rich in protein were employed. After evulsion of the pancreatic ducts there was a gradual failure of utilization of food, whereas the failure promptly followed total pancreatectomy or complete pancreatic fistula, leading to the conjecture that enzymes sufficient for the normal utilization of foodstuffs are absorbed from the obstructed pancreatic ducts. These experimental findings may explain the antithetical results noted in human patients after partial pancreatectomy.

Careful metabolic studies have been reported in only 2 cases of total pancreatectomy in man.<sup>4, 6, 10</sup> In these cases the stools were bulky, light, soft and usually formed. The average daily weight of the stool was two or three times that of normal subjects, largely owing to the excretion of large amounts of fat and protein. The average daily amount of fat eliminated in the stools was five to seven times the amount eliminated by normal persons, and the daily elimination of nitrogen was two and a half to seven times the normal amount.

Of the large amount of fat recovered in the stools, approximately a third was recovered as neutral fat, and the remainder as fatty acid, indicating that, in spite of the total absence of pancreatic enzymes, the splitting of fat was highly successful. The ad-

ministration of pancreatin, a commercial extract of pancreas, in doses of 15 gm per day caused an appreciable reduction in the loss of fat and nitrogen in the feces and a corresponding lowering of the bulk of the stools. On pancreatin therapy, however, there was no significant change in the percentage of nitrogen and fat in the stools, nor was there any change in the percentage of fat recovered as neutral fat and fatty acid. The administration of pancreatin was found to be highly useful in reducing the loss of calories in the stool. In one case 23.9 per cent of the ingested calories were lost in the stool during a test period on a carefully weighed diet.<sup>10</sup> During a second test period on the same diet, but with the addition of pancreatin, the caloric loss was reduced to 12.5 per cent. Although the nitrogen balance of this patient was positive even in the absence of pancreatin, the use of this drug made the maintenance of a positive nitrogen balance much easier.

### *Discussion*

In the present state of knowledge of the physiologic effects of total pancreatectomy in man the following points regarding the postoperative treatment of such cases may be emphasized.

The diabetes that follows total pancreatectomy is relatively mild and, at least in the early postoperative period, appears to be associated with an increased insulin sensitivity. Because of this, hypoglycemic reactions, which may be severe or even fatal should be carefully avoided. Early treatment of the diabetic state should be directed toward the prevention of ketosis rather than to the rigid control of blood sugar levels.

The fatty liver associated with total pancreatectomy in dogs has not been observed in man, but this is probably not a species immunity. Prevention of this disorder can probably be effected by a diet rich in choline. About 2 gm of choline daily is required to prevent fatty liver in pancreatectomized dogs. One egg yolk contains about 0.5 gm of choline, and liver and other glandular meats contain large amounts. In addition, choline chloride and methionine are available commercially and may be used to supplement the diet. In patients who survive for long periods, an occasional check on the level of plasma lipoids, as well as on the size of the liver as noted clinically, should give warning that fatty metamorphosis is taking place.

Because of the poor fat digestion in the total absence of pancreatic secretion, the stools tend to be bulky and frequent, and these changes are more marked the higher the fat content of the diet. For these reasons the postoperative diet should be low in fat, the caloric intake being made up with carbohydrates, which are well tolerated. In addition, pancreatin, in doses of 15 gm daily, should be administered to increase the absorption of fat and protein and to aid in the maintenance of nitrogen equilibrium.

## SUMMARY

A case of diffuse carcinoma of the pancreas treated by total pancreatectomy is presented, together with an analysis of similar cases reported in the literature.

The surgical mortality of total pancreatectomy is high, and the conditions demanding this type of procedure are not commonly encountered. With increasing experience the surgical mortality can probably be reduced to acceptable limits.

The physiologic changes that follow total pancreatectomy are discussed from the standpoint of the diabetic state, the liver changes and the loss of the external pancreatic secretions.

Suggestions for the postoperative care of patients after total pancreatectomy are presented.

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## PULMONARY TULAREMIA IN MASSACHUSETTS

## Report of a Case Due to Tick Bites

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**T**ULAREMIA is a relatively rare disease in New England. The pulmonary form, which is even less common, occurs in Massachusetts, as in the case reported below. It is important to recognize the presence of *Pasteurella tularensis* and its many reservoirs and transmitting agents, for a specific treatment is now available in streptomycin. Otherwise, the pulmonary form is fatal in 40 to 50 per cent of cases. Because of this fact a case of the pulmonary form occurring in a resident of Cape Cod who showed excellent response to streptomycin therapy is reported below.

Tularemia has been reported in every New England state except Vermont.<sup>1</sup> Contact with *Past tularensis* has been noted through the following animals: rabbits, ground squirrels, cats, grouse, mink, sheep, swine and skunk.<sup>2</sup> The great reservoir of infection and the greatest source of human infection is the wild rabbit (jack cotton tail and snowshoe varieties), but owing to the agency of blood-sucking insects common to rabbits and man, cases also result from tick bites and fly bites.<sup>3</sup> The disease should be suspected more strongly in the months from March to October, the period of greatest tick activity. The disease is transmitted and maintained in animals by *Dermacentor andersoni* (the wood tick), *Chrysops discalis* (the horsefly), *Haemaphysalis leporis-palustris* (the rabbit tick) and *Dermacentor variabilis* (the American dog tick).<sup>4</sup> The fact that this disease may result from the bites of ticks or flies or from contamination of the skin or conjunctiva with the tissues or body fluids of infected rodents, flies or ticks is not fully appreciated.

## CASE REPORT

A 68-year-old retired physician, a resident of Duxbury, Massachusetts, was admitted to the hospital on June 9, 1947, because of fever of about 6 days' duration. The patient's residence was important in that he lived on Cape Cod in an area where ticks were especially plentiful in that year. The patient spent much of his time in the woods and fields and for the past month had noted frequent tick bites about his legs. The patient's dog, with which he was in frequent contact, was often infested with ticks, and the patient removed and crushed 10 to 15 ticks daily from the animal. About a week before admission the dog was said to have killed and eaten a rabbit after which the dog seemed sickly for several days. About 4 years previously a neighbor had been hospitalized for an "infected tick bite" and had noted fever and headache for approximately 2 weeks. In the week before admission the patient incurred a number of tick bites on his left leg and picked off a number of ticks each night. The illness began about 6 days before entry with the onset of moderate anorexia and a stinging pain in the left parietal region. These symptoms increased in intensity for the next

few days with the addition of gradually rising temperature to 104°F. Mild shaking chills were noted on the 3rd day of the illness. On the day before admission the temperature remained persistently elevated to 103 to 104°F and the patient showed much mental confusion. There had been no pulmonary symptoms, abdominal pain or change in bowel habits.

Physical examination revealed a well developed, well nourished, elderly man who was markedly confused, lethargic and irritable. There were multiple small (2 or 3 mm.) scabby lesions over the lateral area of the left leg, said to be tick bites; none were ulcerous or appeared infected. The tongue was mildly thickened and covered with a grayish coat. There were no palpable lymph nodes in any area of the body. Examination of the chest disclosed no abnormalities. Neurologic examination was negative. The liver or spleen could not be palpated, but liver dullness extended about two fingerbreadths below the right costal margin.

Examination of the blood revealed a white-cell count of 10,500 with 94 per cent neutrophils. The nonprotein nitrogen was 46 mg. per 100 cc. The agglutination test for undulant fever, the Weil-Felix reaction and agglutinations for *Proteus vulgaris* (strains X, X19 and X2) were negative. Agglutinations for *Escherichia typhosa*, *Salmonella paratyphi* (B), *S. choleraesuis* and *Shigella paradyenteriae* (Sonne and Flexner) were also negative. The heterophil antibody test was within normal limits, and the test for cold agglutinins was negative. Serum sent to the United States Public Health Service for agglutination for *Past tularensis* was reported as negative.

The temperature remained at about 104°F and the pulse remained above 100 for the first 24 hours. The patient was nauseated and vomited several times. He complained of severe frontal headache and was apathetic and mentally confused, but he demonstrated no additional physical signs. Lumbar puncture showed the cerebrospinal fluid to be within normal limits. On the following day the temperature ranged between 102 and 104°F, and the pulse between 90 and 100. The patient still exhibited no pulmonary symptoms, but physical examination revealed dullness in percussion, decreased breath sounds and a few coarse crackling rales over the left base posteriorly. X-ray examination on the following day showed an area of more or less homogeneous increased density in the left lower lung field. There was slight infiltration at both hilum. The appearance was that of pneumonia. The patient was started on penicillin therapy with no beneficial effects and with a temperature consistently elevated to 103 to 104°F, and became more lethargic, apathetic and mentally confused. A repeated cerebrospinal fluid examination was within normal limits. Streptomycin therapy in a dosage of 0.25 gm. intramuscularly every 3 hours was instituted on June 12, and after the patient had received 2 gm. for about 24 hours the temperature and pulse began to fall. The temperature reached normal on June 14 after the patient had received about 4.25 gm. of streptomycin. There was striking improvement of the symptoms of restlessness, irritability and mental confusion, and the patient stated that the severe headache had gone. The white-cell count decreased by 1,000 daily for 5 days, but the differential count consistently showed over 90 per cent of the neutrophil series. Numerous blood cultures demonstrated no growths. Except for a rise in temperature to about 100°F on June 14 and 15 the course of the disease was uneventful, and the temperature and pulse were within normal limits from June 14 to discharge on June 28. The patient had no recollection of the mental confusion and irritability.

The clinical course is demonstrated in Figure 1.

Serum sent to the United States Public Health Service on June 19 was reported as showing agglutination for *Past tularensis* through a dilution of 1:640, agglutination for *Brucella abortus* through a dilution of 1:10 and agglutination

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for *Proteus vulgaris* (strain X19) through a dilution of 1 20 This substantiated the diagnosis of tularemia of the typhoidal type

The pneumonia began to show signs of resolution on June 21, and the patient exhibited rapid improvement until discharge He wished to continue convalescence at home and to be followed by his physician X-ray study of the chest on June 25 demonstrated that consolidation was still present in the left lower lobe There was slight radiolucency medially, suggesting beginning resolution

### DISCUSSION

The public-health aspects presented by this case are important when it is realized that ticks represent a permanent reservoir of possible infection The

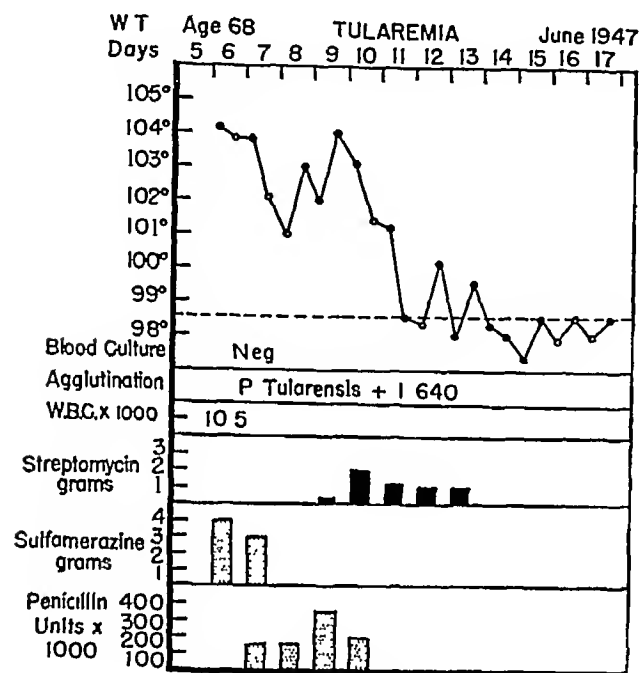


FIGURE 1

female can transmit the organism through the egg to the young, who then harbor them throughout their life.<sup>6</sup> Tularemia may simulate many diseases, such as meningitis, typhoid fever, Rocky Mountain spotted fever, atypical pneumonia, undulant fever and infectious mononucleosis. Owing to its variety it is frequently misdiagnosed as typhoid fever or pneumonia, so that it is essential to think of the disease in differential diagnosis. In Alberta, Canada, physicians include *Past tularensis* as an antigen in routine agglutination tests for typhoid and related organisms, and by this means a small number of cases have been found that might have been missed.<sup>2</sup>

Typhoidal tularemia comprises about 5 per cent of cases of tularemia, and both primary lesions and lymphadenitis are absent.<sup>7</sup> Instead, there is a general systemic infection in which fever and prostration are the outstanding symptoms. In the series studied by Warring and Ruffin<sup>1</sup> it was noted that delirium followed by drowsiness was most marked in the pulmonic type of the disease. In the more

serious of these cases definite areas of consolidation involving one or several lobes appeared. Resolution of the pneumonia began in the third week and was very slow, requiring from five weeks to six months for completion. In a series reported by Francis,<sup>3</sup> a bronchopneumonia type of lesion was the terminal condition in 5 cases, and a lobar-pneumonia type terminated fatally in 2 cases.

In fatal tularemia the most frequent pulmonary lesion is a pneumonia that is basically nodular or confluent nodular in character — sometimes lobar in extent — and involves one to all lobes.<sup>8</sup> The exudate is primarily monocytic and always shows more or less necrosis. In the central portions the septums are usually necrotic, with collagenous, reticular and elastic stroma persisting in considerable measure. Gram-positive cocci are often found in purulent exudates, usually copious. Delicately fibrillar, fibrinous exudates may be identified in some alveoli. The alveolar septums are congested in many cases, both in pneumonic areas and elsewhere. Serous exudation in the other congested areas is common. Vessels frequently show proliferative intimal reactions associated with mononuclear-cell infiltration and perhaps necrosis and thrombosis. The pleura shows fibrinous, fibrinocellular and fibrocaseous exudation in a number of cases.

### SUMMARY

A case of the pulmonary form of tularemia occurring in a resident of Massachusetts and successfully treated with streptomycin therapy is reported.

It is important to recognize the possibility of *Pasteurella tularensis* in the pulmonary form, for this disease is easily confused with others, and a specific treatment is now provided by streptomycin.

Owing to the agency of blood-sucking insects common to wild animals and to man, other cases may result from tick bites or fly bites. Ticks are reported to have shown a decided increase in 1947 in the Cape Cod region and have been noted north of Boston.

This was the first proved case of tularemia reported to the Massachusetts Department of Public Health for 1947. Seven cases in all were reported during 1947 — an unusually high incidence of the disease.

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## PRESACRAL NEURECTOMY FOR DYSMENORRHEA\*

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THIS paper deals with a series of presacral neurectomies performed for relief of dysmenorrhea. A total of 111 operations have been done at the Massachusetts General Hospital and the Palmer Memorial Hospital from 1930-1946. In most cases the neurectomy was combined with dilatation and curettage, a suspension and any other necessary pelvic surgery that the gynecologic situation demanded. These 111 cases can be divided into a group with essential dysmenorrhea and a group with acquired dysmenorrhea. The patients in the former group had severe crampy pain starting shortly after the menarche, with painful menstruation that

relief in 52.6 per cent and partial relief in 21 per cent of cases, and in 26.4 per cent the operation failed, the causes of the dysmenorrhea in this group are presented in Table 2.

In this series there were no deaths. There were only 2 serious postoperative complications severe

TABLE 2. Etiology in Patients with Acquired Dysmenorrhea

CAUSE	No. of Cases
P. inflammation	4
F. uterine	7
P. uterine dysmenorrhea	5
P. appendectomy dysmenorrhea	5
TOTAL	19

TABLE 1. Results of Presacral Neurectomy for Relief of Dysmenorrhea (1930-1946)

RESULT*	PATIENTS WITH ESSENTIAL DYSMENORRHEA	PATIENTS WITH ACQUIRED DYSMENORRHEA
Complete relief	73 (81%)	10 (52.6%)
Partial relief	4 (4.5%)	4 (21%)
Failure	12 (14.5%)	5 (26.4%)
TOTAL	89	19

\*There was no follow-up study in 3 cases.

severely upset their social and economic life, physical examination was negative. The patients with acquired dysmenorrhea had obvious pathologic processes to explain the painful periods. Table 1 gives the results in both groups.

Evaluation of results from the operation were based on a personal follow-up study in the majority of cases and by a follow-up letter in a few. There was little difference in early and late follow-up. If the operation was judged successful at six months the same report was received years later except in 2 cases, which are discussed below. The results were divided into patients with complete relief, those with equivocal or partial relief and those on whom the operation failed.

Complete relief was obtained in 81 per cent and partial relief in 4.5 per cent of patients with essential dysmenorrhea, and there were failures in 12, or 14.5 per cent. In contrast, in the group with acquired dysmenorrhea, in which there was an obvious cause for the pain, presacral neurectomy in addition to other gynecologic procedures gave complete

small-bowel obstructions due to adhesions to the incision in the posterior peritoneum. Lysis of the adhesions was necessary after the intestinal obstruction had been relieved by Miller-Abbott tube. These complications of intestinal obstruction occurred in patients with acquired dysmenorrhea, both of whom had pelvic inflammatory disease.

There was only 1 serious operative complication, a severe hemorrhage from the left common iliac vein when a small branch was avulsed. The rent in the vein was closed, arterial silk being used.

## CAUSES OF FAILURE

Previous reports have adequately demonstrated the efficacy of presacral neurectomy in essential dysmenorrhea, which is now a standard operative procedure in pelvic surgery. However, Tucker<sup>1</sup> reports failures in 11 per cent of cases, Fontaine and Herman<sup>2</sup> in 13 per cent, and Meigs<sup>3</sup> in 15 per cent. Most authors have had about this same percentage of failures. And that is the group upon whom attention should be focused. Of course, the surgeon can calmly accept his 10 to 15 per cent failures and pay no attention to them, or label the patients psychoneurotics and send them to a psychiatrist after operation. In this study major interest was focused on the failures to determine if any measures could be taken to prevent failures in the future. Of great importance is the fact that the cause of dysmenorrhea is not actually known. Anatomic, functional and hormonal studies have not definitely proved what causes crampy pains with menstruation. Rational therapy without knowledge of the etiology is impossible. It is known that these patients are usually sensitive and emotional. Haman<sup>4</sup> has ac-

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curately shown that the pain sensitivity of the patient with dysmenorrhea is low, and the psychiatrists have long emphasized the role of the emotional background of women in this problem. It is our belief that all other means of curing dysmenorrhea should be tried before a presacral neurectomy is performed.

An analysis of the 12 cases in which presacral neurectomy failed to afford relief of essential dysmenorrhea showed that the three possible causes for the failure were psychoneurosis (3 cases), regeneration of the sympathetic nerves (2 cases) and incomplete sympathectomy (7 cases).

The first group comprises three cases judged to be psychoneurotic and emphasizes the importance of the careful choice of the patients. Care was taken in selecting these patients for presacral neurectomy, but the patients who were psychoneurotic, and possibly others in whom the operation failed, were nevertheless subjected to operation. The number of patients with dysmenorrhea who were not judged fit candidates for presacral neurectomy cannot be

If this test is carried out with inhibition of ovulation and the bleeding is still associated with pain, it is safe to assume that the patient has pain on experiencing any vaginal bleeding, and a psychiatrist rather than a surgeon should be consulted. This test is now carried out on all patients who have severe dysmenorrhea, and only those who have complete relief of pain after the estrogen withdrawal are operated upon.

Thirty-five patients were given estrogens and subsequently operated upon (Table 3). The significance of the test is illustrated by the patients who were not relieved of dysmenorrhea after the estrogens and on whom presacral neurectomy was nevertheless performed, resulting in failure. Two of these patients were seen by psychiatrists, and study showed them to be overly sensitive and their dysmenorrhea to be associated with intense emotional difficulties. The third patient had no relief preoperatively with estrogens, and operation was a failure. She too was sensitive, but it was difficult to prove any clean-cut psychoneurotic element in the dysmenorrhea. We believe that this test proves that if the estrogen-withdrawal bleeding is painful presacral neurectomy should not be done.

The second possible cause of failure of this operation is regeneration of the sympathetic nerves. Two cases in which presacral neurectomy failed may be accounted for on this basis. This problem of regeneration of the sympathetic nerves has plagued surgeons interested in other types of sympathectomy. This has been especially true in the dorsal sympathectomies for Raynaud's disease. The early operations done at the Massachusetts General Hospital successfully denervated the upper extremities, but within six months to a year the disease recurred. Sweating and skin-temperature tests showed that the sympathetic nerves had regenerated. Reoperation demonstrated the regenerated nerves. Smithwick<sup>6</sup> circumvented this regeneration in dorsal sympathectomies by attaching a silk cylinder around the cut nerve ends. In splanchnic resections for relief of abdominal pain regeneration also occurs, and relief by sympathectomy may be of short duration. Little mention has been made of this possibility after presacral neurectomy. Regeneration may account for 2 of the failures in our series. Both were considered successful cases with satisfactory relief of pain at their six-month postoperative visits. However, when this follow-up study was undertaken and a questionnaire sent out, 1 patient was three years after operation and the other seven, and both called the operation a failure and said that the dysmenorrhea had returned. Neither permitted reoperation to determine if regeneration had occurred, but that seems to be the best explanation. The infrequency of regeneration after this type of sympathectomy may be due to the fact that a long segment of nerve is removed, which so widely separates the nerve ends that they never rejoin. A reliable

TABLE 3 *Estrogen Test in Essential Dysmenorrhea*

RESULT OF ESTROGEN WITHDRAWAL	SUCCESSFUL PRESACRAL NEURECTOMY	UNSUCCESSFUL PRESACRAL NEURECTOMY
	NO. OF CASES	NO. OF CASES
Painless bleeding	27	5
Painful bleeding	—	3

given, since there is no way in either ward or private practice to obtain the records of all patients with dysmenorrhea. Others have attempted to eliminate the psychoneurotic patients by various methods. Flothow<sup>6</sup> advocated a block of the second and third lumbar segments and also of the superior hypogastric plexus with 2 per cent procaine while the patient was experiencing dysmenorrhea, if relief of pain was produced, presacral neurectomy was advised. He cites an example of a patient with dysmenorrhea who was not relieved by his injection or by spinal anesthesia effective to the nipple line, she was not operated upon. Because of difficulty in obtaining hospital beds we have not used this injection method but have attempted to eliminate the psychoneurotic patients by another test.

This test consists of preventing ovulation by the use of estrogen and then stopping the estrogen and allowing the patients to have withdrawal bleeding. Estrogen-withdrawal bleeding or anovulatory bleeding is painless in the normal, healthy female. A variety of estrogens have been used to stop ovulation. For example, diethylstilbestrol (1 mg daily) may be given for twenty days, starting on the first day of menstruation, ovulation is prevented, and two to eight days after the stilbestrol is stopped withdrawal bleeding occurs and the patient has a painless period.

test to determine the sympathetic supply to the uterus would be of help in this group.

The third possible cause of the failures is an inadequate sympathetomy. Seven cases were so classified because there was no other explanation. By history the dysmenorrhea was essential or primary. In 5 patients the estrogen test before operation completely relieved the pain, and yet presacral neurectomy was a failure. Sympathetic fibers may be missed at two places: the branches from the fourth lumbar ganglion to the presacral plexus often come from beneath the arteries rather than over the anterior surface, and these branches may be missed, more important is the chance of missing a large trunk that goes downward close to the inferior mesenteric and superior hemorrhoidal vessels. Elaut,<sup>7</sup> in a dissection of this area found that in only 25 per cent of the cases is the presacral nerve a distinct, single nerve. In 58 per cent there is a plexus lying between the common iliac arteries; in 16 per cent there are two parallel nerves, and in 2 per cent the nerve is arch shaped. In the last group the nerve may remain close to the inferior mesenteric vessels, and if the sigmoid is in a fairly free mesentery the presacral nerve may be retracted far laterally during the dissection and therefore missed. This anatomic variation may well account for some of the failures of this operation.

#### PREGNANCY FOLLOWING PRESACRAL NEURECTOMY

Follow-up study on this group of 111 cases revealed the fact that 24 patients have had children since presacral neurectomy was performed. Since this operation successfully relieves menstrual cramps we were interested to see what effect the operation had upon first-stage labor pains. Of these 24 patients 8, or 33.3 per cent, experienced no severe cramps with uterine contractions and required no medication. These women and their obstetricians all commented on the lack of pain with labor. Several did complain of low back pain, and all noted the alternate hardness and softness of the uterus. Several patients experienced sensations other than pain with their contraction, such as a tingling sensation at the base of the spine. Two patients complained of discomfort in the rectum, and 1 of intestinal cramps. Two primiparas were delivered without obstetric assistance, since they had not thought that they were in labor until the vertex encountered the perineum. All the patients experienced pain with passage of the baby through the perineum, although this occurred so rapidly that post partum the patient complained of only one brief episode of pain. The force of uterine contractions was normal, and the obstetricians remarked that the labor seemed shorter than that of the average primiparous delivery. Of the 8 women with painless deliveries 6 had essential dysmenorrhea, and 2 had acquired dysmenorrhea due to endometriosis. Seven of the 8 had had complete relief of the dysmenorrhea by

presacral neurectomy. In these 8 cases with painless deliveries the resection of the presacral plexus must have denervated the fundus of the uterus completely. The backaches described are probably due to dilatation of the cervix. Patients, therefore, who have had this operation should be warned that the first stage of labor may be painless and that the physician in charge should be notified when the uterus begins to contract regularly and forcefully.

#### INNERVATION OF THE UTERINE FUNDUS AND CERVIX

Follow-up study also revealed the fact that although the relief of the crampy pains of menstruation was quite successful, 7 patients with essential dysmenorrhea continued to have backache with the periods. The backaches were not incapacitating. This fact that low abdominal cramps were relieved by presacral neurectomy and yet that the backache persisted aroused our interest in the innervation of the fundus and cervix. Pain from the uterus must pass upward in afferent fibers through the presacral plexus to reach the spinal cord. As with other visceral pain the actual pain felt by the patient is referred out along the sensory roots at the same level that the sympathetic fibers reach the cord. Theobald<sup>8</sup> believed that stimulation of the autonomic-nerve endings in the cervix caused a referred pain in the area of skin supplied by branches of the first lumbar nerve and that this pain should be abolished by local anesthesia to the skin area. Labor pain was also interpreted as being a viscerosensory, referred pain. Interruption of the presacral plexus by presacral neurectomy breaks this referred-pain arc. The work of Cleland<sup>9</sup> indicates that the afferent nerves from the fundus reach the cord at the level of the eleventh and twelfth dorsal segments. He found that nupercaine paravertebral block at this level relieved the pain of uterine contractions of women in active labor. Hingson<sup>10</sup> has confirmed this observation since he observed in 3000 cases that caudal anesthesia relieved the abdominal cramps of labor if the anesthetic included the eleventh dorsal segment.

In some women all the afferent fibers may go upward and through the presacral plexus from the cervix to the first dorsal and from the fundus to the eleventh and twelfth dorsal segments. However, since backache is often unrelieved by presacral neurectomy, the afferent nerve supply from the lower part of the uterus may pass outward through some other afferents. Anatomic dissections have shown that the parasympathetic supply to the uterus is from the second, third and fourth sacral segments. This fact may provide a good explanation of why the backaches associated with menstruation are unrelieved by presacral neurectomy and may also account for the backache that the women in labor had after presacral neurectomy, even though they experienced no cramps in 8 out of 24 cases.

Another bit of evidence that may point to variation in the innervation of fundus and cervix was presented by Meigs,<sup>3</sup> who did endometrial biopsies on 2 patients after presacral neurectomy and found that the passage of the curette through the internal os of the cervix caused backache but that scraping of the endometrial cavity caused no pain. He concluded that the cervix had not been denervated. Further studies are under way more accurately to map out the pathways from uterus and cervix to the central nervous system.

#### ENDOMETRIOSIS AND DYSMENORRHEA

We have been interested in searching for tiny areas of endometriosis in these patients with dysmenorrhea. Of the 89 patients with typical histories of essential dysmenorrhea 10 had tiny areas of endometriosis removed from the uterosacral ligaments or from the anterior surface of the uterus near the junction of the uterus and bladder. Endometriosis of this magnitude was only an incidental finding at operation and was not considered as an etiologic factor in the dysmenorrhea. Nine of these patients had complete relief of cramps after presacral neurectomy. In only 1 case to date has the endometriosis progressed. This patient had 90 per cent relief of cramps four years later but complained of sharp pain on the left side. Fixation of the left ovary suggested endometriosis. This observation of endometriosis in 11 per cent of patients with essential dysmenorrhea, whose average age was twenty-four years, makes it apparent that endometriosis may start at an early age. Whether women with essential dysmenorrhea are prone to develop endometriosis has not been ascertained from this study.

#### DYSMENORRHEA FOLLOWING APPENDECTOMY

Included among the patients with acquired dysmenorrhea were 3 whose painful menstruation dated from an appendectomy. Tucker<sup>1</sup> had a similar group of patients, and presacral neurectomy for the dysmenorrhea relieved the cramps. No obvious cause was found at operation on these patients. The histories were very similar. The first patient had no pain with the periods, which had begun at the age of twelve, until she had a normal appendix removed at the age of nineteen. The periods grew steadily more painful postoperatively until a dilatation and curettage and presacral neurectomy four years later. No cause for the pain was found at laparotomy, and presacral neurectomy gave complete relief. In the second patient the periods had started at the age

of fourteen and had been painless until appendectomy at the age of twenty. Thereafter severe cramps began two days before each period and continued for the first two days of the period until relieved by presacral neurectomy two and a half years later. No cause for the cramps was found at operation. In the third patient the periods had begun at the age of thirteen and had been painless until an appendectomy was done for chronic appendicitis at the age of twenty-two. After the operation severe cramps developed, starting one day before the onset of flow and lasting two or three days without let-up. At laparotomy six years later, a small endometrioma was found. The cramps were 90 per cent relieved by presacral neurectomy and resection of an endometrioma of the right ovary. A graduate nurse from this hospital gives exactly the same history of onset after appendectomy, having been free of pain prior to operation. This girl has refused presacral neurectomy. These cases are summarized to draw attention to the phenomenon of pain beginning after appendectomy. Fortunately, presacral neurectomy succeeded in relieving the dysmenorrhea.

#### SUMMARY

A series of 111 cases of presacral neurectomy for dysmenorrhea are reviewed. Complete relief was obtained in 81 per cent of cases of essential and 52.6 per cent of acquired dysmenorrhea. There were 12 failures after presacral neurectomy for essential dysmenorrhea. These failures are accounted for on the basis of either regeneration of sympathetic nerves, incomplete operation or dysmenorrhea as a manifestation of a psychoneurosis. Twenty-four women had babies postoperatively, labor was painless for 33.3 per cent.

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## PRIMARY FRIEDLANDER-BACILLUS PERITONITIS\*

## Report of a Case

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**PRIMARY** unexplained infection of the peritoneum by the Friedländer bacillus (*Klebsiella pneumoniae*) is a condition of evident rarity. The case reported below (the second in the medical literature) describes a disease that is a distinct though little known clinical entity. Additional reports will aid in delineating possible similarity to the better known idiopathic pneumococcal and streptococcal peritonitides of infants and children.

## CASE REPORT

E. I., an 8-year-old girl of Irish descent was referred to the hospital in April, 1943, by her family physician with the diagnosis of appendicitis with perforation. The immediate history dated to 4 days before admission when she had complained of abdominal cramps and had vomited and retired to bed. There had been no stool for 3 days the appetite had been very poor until the morning of admission and since then the patient had eaten nothing. The abdominal cramps diminished somewhat after the 1st day but on the day of admission returned with marked severity throughout the entire abdomen and the child vomited several times. An enema was given on the afternoon before admission with slight relief from pain after expulsion of a small amount of gas. There had been some burning pain with urination on the day of admission.

The past history indicated no similar previous illnesses. The patient had been suffering from a fairly severe upper respiratory infection during the 2 weeks prior to admission. No previous symptoms could be referred to the gastrointestinal tract, urinary tract or gynecologic disorder. The patient had had measles and chicken pox in earlier childhood. A younger sister and the parents had been well during the period of the patient's illness. The remainder of the family history was noncontributory.

Physical examination showed the patient to be acutely sick, pale, listless and poorly oriented and breathing rapidly and complaining of generalized abdominal pain. The head was essentially normal. There was a very slight injection of the oropharynx the tonsils were not remarkable. A few small, slightly tender lymph nodes were palpable in the neck axillae and groins. The chest was clear resonant and symmetrical and normal by roentgenogram. The abdomen was distended, tense and tender in all quadrants, especially the lower. No masses were palpable. There was tympany throughout. No peristalsis was audible. Rectal examination demonstrated tenderness in all directions and withdrawal of the examining finger was followed by expulsion of gas and enema fluid.

The temperature was 103.8°F by rectum the pulse 140 and the respirations 28.

The white-cell count was 3600 with 64 per cent neutrophils, and when repeated in 2 hours, 3200 with 56 per cent neutrophils. The hemoglobin was 68 per cent (9.5 gm per 100 cc. of blood). Clear bile-stained vomitus was guaiac negative. The urine was straw colored clear and acid with a specific gravity of 1.014 no albumin or sugar and no remarkable sediment.

A diagnosis of generalized peritonitis due to a perforated appendix or idiopathic pneumococcal infection was considered.

Immediate treatment consisted of placing the patient in an oxygen tent in restraints and allowing nothing by mouth

except cracked ice. Codeine phosphate (0.06 gm.) and sodium luminal (0.06 gm.) were given subcutaneously as often as needed for pain and restlessness. A Levine tube was passed into the stomach which was emptied of a small amount of fluid and was left for open dependent drainage. The patient was immediately given 1500 cc. of 10 per cent dextrose in physiologic saline solution with 2 gm. of sulfanilamide in solution as prontosil and this was followed with 300 cc. of cross matched citrated whole blood on the evening of admission. A Miller-Abbott tube (size No. 12 Fr.) was passed 75 cm. and was to be advanced on the following morning the patient pulled the tube out, and it was not reinserted.

On the 1st hospital day the patient was listless and less well oriented than on admission and appeared to be in poor condition. A repeated examination of the blood showed 8.5 gm. hemoglobin per 100 cc. and a white-cell count of 5100 with 54 per cent neutrophils. Operation under local anesthesia for drainage of pus from the lower abdomen and implantation of sulfanilamide was elected. A small right lower-quadrant, muscle splitting incision was made and approximately 500 cc. of yellow acid-smelling fluid, of the consistency of thick broth was expelled from the lower abdomen as though under pressure. A large rubber tube was inserted in the pelvis and 8 gm. of crystalline sulfanilamide was implanted in the lower abdomen through the wound. This procedure was tolerated well.

The patient was treated on this and the 3 succeeding hospital days with continuous daily infusions of 2500 cc. of 10 per cent dextrose in physiologic saline solution in addition to the infusion of 250 cc. of cross matched citrated whole blood every 12 hours. The sulfanilamide level on the day after operation was 11.4 mg per 100 cc. and thereafter sodium sulfadiazine in the continuous infusion was given in a dosage of 3 gm. per day. Sulfadiazine levels between 10.4 and 22 mg per 100 cc. were subsequently recorded. The carbon dioxide combining power varied between 41.6 and 62 vol. per cent and the urea nitrogen between 6.5 and 8.6 gm per 100 cc. The hematocrit on the 3rd hospital day was 38 per cent. Hemoglobin determinations on the 1st, 2nd and 3rd days were 8.5, 10.5 and 10 gm per 100 cc. of blood. The white-cell count mounted to 16,700, with 88 per cent neutrophils, by the 2nd hospital day but fell to 10,400 with 68 per cent neutrophils on the 3rd day. The urine output was estimated to be satisfactory with at least 500 cc. each day. A culture of pus from the abdominal cavity at the time of operation grew out Friedländer bacillus in pure culture. A blood culture on the day of death was sterile.

Although some clinical improvement was noted in the hours immediately after operation, the patient's condition became progressively worse, and the temperature of 102°F mounted to 104°F 6 hours before death. The pulse mounted progressively to 176, and the respirations became more rapid shallow and thoracic in character, remaining between 35 and 40 during the last 2 days. Signs of atelectasis and scattered coarse rales were noted during the last 2 days and on the 4th hospital day the patient became comatose, aspirated vomitus and expired.

**Autopsy.** Post mortem examination performed by Dr. Walter W. Brandes revealed a well developed and well nourished child weighing 25 kg. There was moderate cyanosis of the face and fingertips. The abdomen was moderately distended and a recent 8-cm long McBurney incision was present.

The peritoneal cavity contained 1000 cc. of turbid fluid with numerous soft, gray masses of exudate rich in fibrin. The peritoneal surfaces were hyperemic, and thick deposits of this exudate were present over them as well as over the upper surface of the liver. The appendix was also partly

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covered. No evidence of rupture or perforation of any viscus was found.

The pelvic organs showed peritoneal hyperemia and depositions of fibrinous exudate. The fallopian tubes were patent, and their lumens were free of exudate. The cavity of the uterus disclosed no evidence of inflammation. The ovaries were not enlarged.

Other organs demonstrated changes associated with marked inflammatory reactions. There was acute splenic swelling, parenchymatous degeneration of the liver and kidneys and passive hyperemia. Medullary portions of the adrenal glands were softened. The mesenteric lymph nodes were moderately swollen, soft and hyperemic. The small bowel presented only the serosal change mentioned. The mucosa of the cecum and ascending colon was noticeably swollen, it was soft, pale, and grossly edematous. There was no ulceration. The rectum was not noticeably altered. The pancreas was normal, and the gall bladder and bile ducts were not remarkable.

Examination of the pleural cavities revealed a small amount of fibrin present on the diaphragmatic surfaces. The thymus, mediastinum, great vessels, pericardium and heart were not remarkable. The trachea and major bronchi contained a small amount of gastric contents. Their mucosa was bluish red. The lungs revealed no gross evidence of pneumonia. They presented peripheral collapse, which was most noticeable in the lower lobes, more on the left side, involving two thirds of the left lower lobe.

Microscopical changes were those of an acute fibropurulent inflammation of the peritoneal surfaces. The exudate was composed of fibrin and leukocytes, fibrin predominated. Some of the polymorphonuclear cells were swollen and vacuolated. The subserosal layer of the peritoneal surfaces revealed marked hyperemia and edema, the edema sometimes extending to the submucosa of the bowel. There was no evidence of primary inflammation of the appendix, uterus, fallopian tubes or ovaries or of the gall bladder.

Cultures of the peritoneal exudate demonstrated a pure growth of Friedländer bacillus, contents of the lumen of the terminal ileum revealed the presence of this organism along with *Escherichia coli* and an unidentified member of the Clostridium group. A throat culture failed to demonstrate Friedländer bacilli.

Morphology of the cultures, cultural characteristics and morphology of the organism were those of Friedländer bacillus. Intraperitoneal mouse inoculations resulted in death after 12 hours, with demonstration of the organism in the peritoneal smear. Serologic typing of the organism (Julianella) was not performed.

### DISCUSSION

The post-mortem examination failed to reveal the portal of entry of the infection or any primary site. Changes in the bowel, including the marked edema of the proximal colon, were, in all likelihood, secondary to the peritonitis. The presence of the infecting organism in the bowel lumen suggests that site as its source. In some unexplained manner the peritoneum became infected. Review of the literature disclosed a single case of probable primary peritonitis due to Friedländer bacillus reported in England by Cook<sup>1</sup> in 1931. As in the case presented above, the patient was a young girl (nine years old), she had an acute tonsillitis with exudate, and redness of the vagina, as well as generalized peritonitis when she was first seen five hours before death. This patient was treated by drainage of the lower abdomen performed under local anesthesia. Pus was described as dark and foul. Details of autopsy examination offered were throat and peritoneal culture (showing *K. pneumoniae*) and a description of a generalized peritonitis similar to that in the case presented above.

McDonald and Klingon<sup>2</sup> reported a case of peritoneal infection as "primary peritonitis caused by Friedländer's bacillus" in 1946, and considered it to be the first of such reports, apparently overlooking Cook's case. A review of their report leads to the conclusion that their case is not acceptable as a primary peritonitis of the etiology stated. The patient was a forty-seven-year-old man with a medically complicated past history and a recent history suggestive of a perforative lesion in the gastrointestinal tract. The patient was operated upon a few hours after the onset of an abdominal crisis, the culture of pus grew out not only a Friedländer bacillus but also beta-hemolytic anaerobic streptococci. The presence of a mixed bacterial infection, as well as certain other inconsistencies in the diagnosis, suggests that the case of Cook and the one reported above actually represent the only reported primary idiopathic infections of the peritoneum by the Friedländer bacillus.

### TREATMENT

Aside from the merits of drainage vs nondrainage and intraperitoneal use of sulfonamides, rational therapy for this condition with means now at hand must be predicated on early diagnosis and the most likely antibacterial agents used. The technic reported by Ladd and Gross et al. as used at the Children's Hospital, Boston, with diagnostic smear of peritoneal exudate obtained by early laparotomy, would accomplish differentiation of the Friedländer bacillus from the streptococcus, pneumococcus and the mixed infection of fecal peritonitis. The Friedländer bacillus is easily recognized as an encapsulated, short, plump, gram-negative rod and is present, in large numbers in exudates of peritoneal infection so caused. Characteristic encapsulation is striking in these smears and is easily seen with ordinary aniline (dye) stains.

Studies and reports in recent years have indicated that sulfadiazine is probably the most effective sulfonamide drug for use against the Friedländer bacillus. Sesler and Schmidt<sup>3</sup> have shown clearly that this is true both in vitro and in animal experiments, although the variation in reaction of different strains of the organism is emphasized. Ransmeier and Major<sup>4</sup> assembled comparative statistics of mortality to show that sulfadiazine improves the outlook in the highly fatal Friedländer meningitides. Heilman<sup>5</sup> and others have shown that streptomycin may be more effective than any other antibacterial agent.

Penicillin is not effective in physiologically feasible concentration. However, Heilman and others found such variation in sensitivity to streptomycin (four thousand times the original concentrations in vitro) of different strains that one must conclude that some cases cannot be benefited by streptomycin administration. When possible, preliminary assay of the effect of either sulfadiazine or streptomycin in vitro

would aid in anticipating the most successful treatment. Serologic and bacteriologic classification of the organism is of no value, since there is no correlation between type and either sensitivity to sulfadiazine and streptomycin or virulence and occurrence as a pathogen. Organisms are most often Julianelle Type A, but virulent infections are also caused by types B and C and those of Group X.

### BACTERIOLOGY

The Friedländer bacillus is grossly related to the coliform group. It is known to be a common organism of the bacteriologic flora of the intestinal tract. Kendall,<sup>6</sup> whose study seems to have included *Aerobacter aerogenes* as well, found that these organisms were common in the intestines of infants but not in those of adults, whereas Dudgeon<sup>7</sup> cultured the organisms in the feces of 55 per cent of a large group of patients, most of whom had some lesion or disease of the oropharynx or of the intestinal tract. Baehr, Schwartzman and Greenspan<sup>8</sup> state that it is a more frequent inhabitant of the intestine than elsewhere and is rare as a primary pathogen in the respiratory tract, where it usually appears as a secondary invader. Most textbooks of bacteriology state that this organism is found chiefly in the respiratory tract in man. The Mt Sinai workers, however, report a unique and significant study of 61 cases of peritonitis caused by this organism alone or in conjunction with other organisms, in all these cases the portal of entry was demonstrated (mostly perforated appendix or bowel). The authors further described abdominal infection from liver abscess and biliary-tract, urinary-tract and pelvic infection, so that of 198 consecutive cases reviewed, 163 infections due to the Friedländer bacillus were present in the abdomen, pelvis or urinary tract. This report has stimulated comment<sup>9</sup> and greatly clarifies the understanding of the pathogenesis of infections due to the Friedländer bacillus.

After Friedländer<sup>11</sup> described the organism that bears his name as the virus causing lobar pneumonia (from post-mortem lung cultures in 8 cases) and designed it as "*Klebsiella pneumoniae*," the error of his conclusion was soon demonstrated by description of the pneumococcus as the far more common pathogen in such cases. However, even now the term "pneumobacillus" is a common synonym for the official (Bergey) *K. pneumoniae*. It has been suggested that the long-delayed recognition of the true natural occurrence of the Friedländer bacillus as a pathogen may be due in part to cultural and morphologic similarity to the colon bacillus, because of which in modern rapid hospital bacteriology the Friedländer bacillus is often reported as *Esch. coli*, and to the larger attention accorded culture and other bacteriologic study on medical wards (and in cases of chest infection) than on surgical patients (with perforative lesions of the gastrointestinal tract).

In this connection, the excellent studies of Ostermann and Rettger<sup>12,13</sup> on comparison of the organisms of the Friedländer and coli-aerogenes groups are cited. These authors indicate that, whereas there may occasionally be erroneous identification by ordinary biochemical reactions and cultural characteristics (in particular when virulent nonencapsulated forms of Friedländer and *Aerobacter* organisms or colon bacilli that are encapsulated are encountered), no valid criteria exist for the differentiation of the organisms that can be applied consistently to all cases. The authors state that there has been a tendency to rely on the origin of a culture as a material aid in its identification and point out that in their study, cultures of *Esch. coli* and *A. aerogenes*, as well as the Friedländer bacillus, came from similar and diverse natural sources. They consider that further study by serologic means will provide a more complete explanation of interrelations.

Examination of the bacteriology in reports cited reveals that in Cook's case, only a statement that the cultures showed a Friedländer bacillus is offered, in the case reported above, the morphology, mouse virulence and biochemical characteristics (admittedly variable) were the basis for identification, and in the series of Baehr, Schwartzman and Greenspan, the criteria were "Gram negative bacilli showing well defined capsule and typical 'gum drop' and stringy colonies on solid media were considered to belong to the *B. friedländer* group, provided these characteristics persisted for at least three to four passages through artificial media." Thus, the certainty that these authors were not in some cases dealing with *A. aerogenes* is by no means established.

Ostermann and Rettger believe that serologic typing is most conclusive in identifying strains of Friedländer bacillus that can be so treated, and studied the antigenic relation of the Friedländer bacillus, *A. aerogenes* and *Esch. coli*. They emphasize the occurrence of variation in colonial morphology, group antigenic relation and the exceptions that seem to occur when any set of standards for identification are applied. The problem awaits further elucidation, even to the study of the normal and pathologic occurrence of the Friedländer bacillus, identified with means now at hand.

If the findings of the Mt Sinai workers can be substantiated in the light of these conditions, a amendment to the older teaching that Friedländer-bacillus infections occur most commonly above the diaphragm and redesignation of the organism as either *Bacillus friedländer* or *B. mucosus capsulatus* are suggested. The list of primary infections caused by this organism gleaned from the literature includes those in the sinus, mastoid and middle ear, throat, lungs, heart, pericardium and intravascular sites, peritoneum, biliary tract and liver, perinephric space, kidneys and lower urinary tract, pelvic organs of the female, and prostate, vesicles and epi-



didymis of the male, brain meninges, bone and soft tissues of the extremities

### SUMMARY

A case of primary generalized peritonitis due to the Friedländer bacillus, the second in the medical literature, is reported

Some aspects of the treatment of such infection with newer agents are briefly discussed

Attention is again directed to the similarity in occurrence and pathogenicity of Friedlander bacillus and *Escherichia coli* and to the probable error of considering the Friedländer bacillus to be primarily a pathogen in the respiratory system The problem of bacteriology and identification is discussed

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## MEDICAL PROGRESS

### ABDOMINAL SURGERY (Concluded)

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#### THE DUODENUM

Shapiro and Robillard<sup>61</sup> discuss anomalies of the blood supply of the duodenum There are many variations in the vascular arrangement in this region, and unless these are recognized, avascularization of the duodenal stump following gastrectomy may result in necrosis and leakage Avoidance of this complication is simple if the surgeon frees the duodenum from the pancreas only enough to allow an adequate turn-in of the duodenal stump This is best accomplished if the adherent and inflammatory area about the ulcer site is approached after the stomach has been transected Freeing the duodenum distal to the ulcer as a first step in the procedure is more apt to lead to avascularization with subsequent necrosis

Ferguson and Cameron<sup>62</sup> advise giving the patient with a diverticulum of the duodenum a drink of barium the night before operation The barium coats the lining of the diverticulum, making it easier to find They point out that such lesions are a herniation through the muscular coat of the bowel and occur usually on the mesenteric border between two blood vessels They recommend free dissection and inversion of the diverticulum, repair-

ing the defect in the musculature with interrupted fine silk sutures

Mahorner and Kisner<sup>63</sup> suggest the inflation of the duodenum with air introduced through a 22-gauge needle on a 20-cc glass syringe, to outline diverticula They advocate free dissection and amputation distal to a small clamp applied to the neck of the diverticulum The mucosa is inverted with a 00 chromic catgut suture, and the muscularis with interrupted fine silk or cotton sutures

All the authors cited above agree that the incidence of diverticula of the duodenum is from 1 to 2 per cent of the adult population The majority of these lesions are symptomless or cause dyspepsia easily controlled by dietary measures A small percentage of patients may have sufficient disability to warrant corrective surgery

Acute perforation of duodenal ulcer is again discussed by Graham<sup>64</sup> In 125 consecutive cases treated at the Toronto General Hospital the operative mortality was 64 per cent The author considers chemical and nutritional imbalance, rather than bacterial peritonitis, to be responsible for the serious shock-like state of the patient after perforation He believes that better results can be obtained if the patient in poor condition is given supportive therapy for a few hours prior to surgery Attention is called to nature's tendency to seal the

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perforation by a deposit of fibrin.<sup>3</sup> He stresses the importance of aiding this process by the application of a tab of omentum to the area. Concomitant gastroenterostomy, gastroduodenostomy, gastric resection, intraperitoneal use of sulfonamides and drainage of the abdomen are all condemned.

Bobmansson<sup>66</sup> has presented an excellent discussion of massive hemorrhage from peptic ulcer. The problem is a combined one that concerns the internist as well as the surgeon. Careful evaluation of such cases should be made to determine whether or not conservative or radical treatment is indicated. Early operation is advocated if the roentgenogram shows a crater or if there is a history of previous perforation or if the ulcer is known to be chronic and when shock-level bleeding cannot be readily combated by blood transfusions. Radical operation is recommended if any surgery is done, since this is the only feasible approach to blood vessels leading to the ulcer area, and exact hemostasis is necessary. By the combined efforts of medicine and surgery, the mortality was reduced from 9.1 per cent in 1939 to 5.1 per cent in 1945. The operative cases were decreased during this period from 45 to 7 per cent of the total. The mortality of the conservatively treated group was reduced from 6 to 5 per cent, and the operative mortality fell from 13 to 5.1 per cent.

Heuer<sup>66</sup> reports that 8 per cent of 337 patients admitted to the New York Hospital with acute massive bleeding from peptic ulcer died. Fifteen per cent of the cases were of the type that would have resulted fatally had not operative interference been carried out. He stresses early decision for or against surgical intervention. The mortality was 10 per cent in patients operated on early in the episodes, as compared with 70 per cent when the operation was undertaken after several days of bleeding. He also emphasizes the necessity for radical gastrectomy in these cases, stating that palliative operations are useless.

There is some tendency to operate early in more cases of acute massive bleeding from gastric and duodenal ulcer than formerly. With the marked reduction in the operative risk now evident, there is a definite argument in favor of such an attitude. The fact that the younger patients in this group almost invariably cease to bleed under conservative treatment, whereas the older patients more frequently died of hemorrhage during the episode, has been stressed.<sup>67</sup> So far, surgeons have not been able to bring about a successful outcome very often if the operation is undertaken after several days of bleeding. It is true that most of the patients operated upon within seventy-two hours of the onset of hemorrhage can be brought through safely. Much time could be saved the younger patients by a radical attack as soon as shock had been properly controlled, since most of them should be operated

upon eventually to prevent recurrences of these disturbing bouts of bleeding.

Dragstedt et al.<sup>68</sup> express their present attitude concerning transabdominal vagus resection for ulcer. Sixty-one transthoracic and 109 transabdominal vagotomies form the basis of their thesis. They also confirm previous reports that the vagus nerves have several anatomic variations but believe that all these cases lend themselves to the abdominal approach. They have no hesitancy in combining vagotomy with gastroenterostomy or gastroduodenostomy when there is evidence of cicatricial obstruction. Eighteen out of their total of 170 cases showed evidence that the vagi had not been completely interrupted. Reoperation with resection of retained vagus fibers resulted in relief in 2 patients. Six of the 18 had recurrence or persistence of ulcer symptoms. The patients were maintained on gastric suction for from four to six days after vagotomy, and a normal diet was not tolerated for from two to eight weeks.

Fallis and Warren<sup>69</sup> state that anastomotic ulcer occurs in 15 per cent of patients having gastroenterostomy for duodenal ulcer. The stomal ulcer always occurs in the efferent loop of jejunum opposite the anastomosis. Patients who have had perforation or bleeding from the original ulcer are prone to have the same manifestation in the new lesion. The authors consider medical treatment unsatisfactory for these patients and, at the time of their report, believed that subtotal resection of the stomach, with aseptic technic and short-loop retrocolic anastomosis, was the treatment of choice.

#### THE SMALL INTESTINE

Pemberton and his associates<sup>70</sup> bring to mind the rare lesion described by George Whipple in 1907, termed "lipodystrophy." They believe that only 14 cases have so far been reported and add 3 cases observed at the Mayo Clinic. The syndrome in brief is that of abdominal pain and weight loss, a doughy-feeling mass in the abdomen and steatorrhea. The findings are those of mesenteric thickening with engorged lymphatic vessels. Microscopical examination of the fatty tissue of the mesentery shows leukocytes and giant cells. X-ray and bile-salt therapy has been suggested but is of questionable value. The usual course is one of long duration and gradual disintegration.

Lazarus and Marks<sup>71</sup> discuss benign intestinal tumors of vascular origin, finding 38 cases reported in the literature. These tumors vary from capillary nevi to cavernous hemangiomas. It is probable that some of the cases of obscure gastrointestinal bleeding can be accounted for on the basis of these lesions which are often small and easy to overlook. The authors describe a patient who continued to bleed after four operative attempts had been made to remove the vascular tumors, which are often multiple and may involve the entire intestine.

Saltzstein and Rao<sup>72</sup> report the history of a patient who bled massively from the intestine. Exploration revealed a surgical sponge, which was encysted but had eroded a 1-cm area of the ileum. The patient had been operated on twenty-five years previously for a pelvic complaint and twenty-three years before for intestinal obstruction. The authors quote Crossen and Crossen,<sup>73</sup> who collected 250 cases of foreign bodies in the abdomen, as stating that these usually gravitate to the pelvis and become extruded through the bowel, vagina or bladder. Fourteen of the 250 foreign bodies had remained within the abdomen for five or more years, and these were all encysted.

A case of leiomyoma of the jejunum operated on for massive hemorrhage supposedly from duodenal ulcer is reported by Marshall and Welch.<sup>74</sup> The lesion was located 15 cm beyond the ligament of Treitz and was successfully resected.

Botsford and Seibel<sup>75</sup> have reported all the tumors of the small intestine, exclusive of those arising from the papilla of Vater and the pancreas, encountered at the Peter Bent Brigham Hospital, Boston, from 1913 to 1946. Sixty-five primary tumors were found, of which 33 were malignant and 32 were benign. The malignant tumors were classified as adenocarcinoma in 18, lymphosarcoma in 13 and carcinoma in 2 cases. The benign lesions were lipomas, adenomas, leiomyomas and fibromas in that order of frequency. There were 10 in the duodenum, 14 in the jejunum and 41 in the ileum. Half the lesions were apparently symptomless and were found incidentally. The observations are in accord with the experience of others that adenocarcinoma is more common in the high intestine and that sarcoma is more often found in the ileum.

Rabinovitch et al.<sup>76</sup> found 15 cases of sarcoma of the bowel in the records of the Jewish Hospital, Brooklyn, New York, in a twenty-five-year period. They state that this lesion has a ratio to carcinoma of 1:55 in the small intestine, 1:275 in the colon and 1:577 in the rectum.

Patent omphalomesenteric duct and its relation to the diverticulum of Meckel is discussed by Kittle and his co-workers,<sup>77</sup> who present an excellent review of the history and embryology of this lesion. Although Meckel's diverticulum occurs in from 1 to 2 per cent of the populace, a patent omphalomesenteric duct has been reported in only 128 cases. The authors cite 3 cases of their own and call attention to the importance of the lesion in producing intestinal obstruction when a loop of small intestine prolapses through the patent ductus. For this reason, they advise operative correction of this congenital defect whenever the diagnosis is made.

Another good review of the literature on Meckel's diverticulum has been made by Haber.<sup>78</sup> He studied critically 23 case histories at his disposal and emphasized the significance of this lesion in the differ-

ential diagnosis of patients with apparent intestinal obstruction.

Devine<sup>79</sup> presents an excellent discussion of paralytic ileus. From the study and observation on 43 cases, he deduces that this syndrome can be divided into three stages. In the first stage, there is normal bowel activity, and the intestine can respond to stimulation. During the second stage, there is disordered movement and drugs that stimulate peristalsis, as well as enemas, will do no good but will increase discomfort and distention, thereby hastening the third stage. In this last phase, there is loss of intestinal motility with the development of full-blown ileus. Experiments following intestinal intubation with various local applications and drugs led to these concepts. Heat and turpentine stupes had no effect on bowel movements. Barbiturates decreased peristalsis and bowel tone. Penicillin and sulfonamides did not affect motility. Overdistention of the stomach produced loss of bowel tone and movement. Stimulation of the colon with enemas also stimulated the small intestine. Devine advises no cathartic before operation, gentle handling of the intestine, limitation of fluids by mouth for twelve hours post-operatively because of swallowed air, atropine and barbiturates to be kept to a minimum, the liberal use of morphine and no stimulation of the intestine by drugs or enemas until peristalsis is normal. Miller-Abbott intubation and intravenous fluids offer the best treatment for paralytic ileus when it occurs.

Watt and Harner<sup>80</sup> report 3 cases of intestinal obstruction from bezoars. Two of these were from the ingestion of persimmons, and the other from hair. All were found in the terminal ileum, and all the patients recovered after surgical removal of the bezoars.

An interesting case of intestinal obstruction from the rapid ingestion of five oranges in a man with a previous Polya operation is reported by Baumeister and Darling.<sup>81</sup> The orange pulp had collected in the ileum and had to be removed surgically to relieve the obstruction. I have encountered a similar case in an edentulous man with a previous gastroenterostomy who admitted swallowing a peeled orange in two halves. At operation it appeared that these sections had come together and lodged in the usual narrow area of the terminal ileum.

Eliason and Welty<sup>82</sup> review the records of cases of intestinal obstruction at the University of Pennsylvania Hospital in a period of ten years. Patients treated before the Miller-Abbott tube was used gave a mortality rate of 50 per cent, as compared to 11 per cent in recent years. The average age of the survivors was forty-four years, and that of those who died was fifty-nine years. The mortality in patients with cancer was 34 per cent, in strangulated femoral hernia, it was 31 per cent, and in strangulated inguinal hernia, it was 5 per cent. Excluding cancer

and strangulation obstruction in 159 consecutive cases, there was 1 death in the recent series.

Seven children with strangulated, nonreducible intussusception were treated by resection and primary anastomosis by Dennis,<sup>83</sup> with no deaths. He advocates end-to-end anastomosis with one row of silk Halsted mattress sutures, and points out that the inflammatory reaction occurring about catgut sutures may well account for edematous obstruction and failure.

Retrospect intussusception is discussed by Thorek and Lomer.<sup>84</sup> They report a case of a fifty-nine-year-old Negro who developed a gradual obstruction from an adenocarcinoma of the cecum. At operation the cecum was invaginated into the terminal ileum, which was dilated to one and a half times the size of the transverse colon. They quote Groper's<sup>85</sup> classification of retrograde intussusception as follows: jejuno gastric, enteric, cecoileal and colic.

Garlock<sup>86</sup> has analyzed 200 cases of regional ileitis treated at the Mt. Sinai Hospital, New York City. The acute phase of the disease is nearly always diagnosed and operated on as acute appendicitis. The patients do surprisingly well, and in many cases the disabling chronic phase of the disease does not follow. If remissions last for a number of years after an acute onset, the patient rarely has a recurrence. Although some patients with chronic cases do well on conservative measures and are not disabled by the disease process, the majority of them develop fever, weight loss, fistulas and abscesses. This tendency makes it justifiable to consider them as primarily a surgical problem. Ileotransverse colostomy, following a division of the ileum with closure of the distal segment, gives the best results. There was no mortality after this procedure, and only 10.5 per cent of patients developed recurrences requiring resection of the terminal ileum and right portion of the colon. Ileocolostomy in continuity not only failed to improve these patients but also made them worse. One-stage resections were associated with a mortality of 16.3 per cent and recurrences of 15.4 per cent. Two-stage resections resulted in 12 per cent mortality and 28.6 per cent recurrences. Garlock believes that the disease starts in the ileum and not in the lymphatic vessels. He calls attention to the fact that fistulas close spontaneously after they are excluded by ileotransverse colostomy.

#### THE COLON

Beck and Hopkins<sup>87</sup> report 5 cases of diverticulitis of the cecum. Four patients had acute manifestations and were operated on with the diagnosis of acute appendicitis. Two were treated by simple resection of the diverticulum, 1 by right colectomy and primary ileotransverse colostomy, and 1 by a resection of the Mikulicz type. One case was diagnosed preoperatively, and the diverticulum excised after a planned cholecystectomy.

Two cases of diverticulitis of the cecum and ascending colon are reported by Fairbank and Rob.<sup>88</sup> They discuss the difficulties in differentiating these lesions clinically from carcinoma. Both patients were treated by right hemicolectomy with recovery.

Anderson<sup>89</sup> reviews this subject and finds 91 reports of acute diverticulitis of the cecum in the surgical literature. Diverticula in the colon are found in 5.7 per cent of roentgenograms and 6.9 per cent of autopsies at the Mayo Clinic. In 700 cases of surgical diverticulitis treated there, only 9 were in the right portion of the colon. Eight case histories are given in the report. Resection of the right portion of the colon or cecum had been carried out in one third of the cases, probably because they could not be distinguished from perforated carcinoma. The preoperative diagnosis in 84 of the 91 cases reported was acute appendicitis. The operative mortality in the whole group was 6.4 per cent. Local procedures when they could be done carried less risk than bowel resection. The average age of these patients was thirty-nine years and two months. This is striking, since the more common sigmoid diverticulitis is found in a much older age group.

Pemberton et al.<sup>90</sup> have reported the results obtained in the surgical treatment of 389 patients with diverticulitis of the sigmoid colon. Two hundred and forty-five of these were treated between 1908 and 1940, with a mortality of 14.7 per cent. One hundred and forty-four were treated from 1941 to 1945, with a mortality of 4.2 per cent. The authors deduce from their experience that proximal colostomy should be done in all acute cases. They advise resection of the diseased area by the Mikulicz principle six to twelve months later. They attribute the better results obtained in the second group of patients largely to the use of sulfonamides.

Scott and Serenati<sup>91</sup> have analyzed the records of 31 patients with megacolon occurring in 250,000 admissions to the Strong Memorial Hospital, Rochester, New York. These cases are divided into four categories: neurogenic, congenital with organic obstruction, functional with obstruction, and those with extrinsic metabolic effects such as avitaminosis, malnutrition and hypothyroidism. The congenital obstructions are relieved surgically without further consideration. Conservative measures are carried out in all other cases. Parasympathetic drugs, enemas and mineral oil are given a thorough trial. Spinal anesthesia may bring about a dramatic temporary effect, and when this occurs, sympathectomy is indicated. In some cases, in which there seems to be a more lasting effect from spinal anesthesia, a continuation of conservative treatment is justified. If colectomy is done, the authors advise only a left hemicolectomy and a lateral anastomosis to produce the widest possible stoma.

Young and his associates<sup>92</sup> report 7 cases of volvulus of the cecum, which they consider to account for slightly more than 1 per cent of all cases of intestinal obstruction excluding external hernia. The authors believe that the diagnosis can often be made by a typical appearance observed in the scout roentgenogram of the abdomen. A carefully given barium enema may be necessary to confirm the diagnosis. If the lesion is early and the bowel viable, detorsion and cecostomy are advised. The fixation of the cecum by inflammatory reaction about the cecostomy prevents recurrence. Resection must be done if vascularity of the bowel has occurred. Exteriorization of the Mikulicz type is usually the safest procedure in such cases.

Volvulus of the sigmoid colon is discussed by Bruusgaard,<sup>93</sup> who states that this condition is much more common in the eastern European countries than in western Europe and the United States. He attributes this to the high vegetable diet, particularly during the war years, necessary in eastern Europe. Apparently volvulus of the sigmoid accounted for from 30 to 50 per cent of intestinal obstructions in these countries as compared to 10 per cent in the United States. Ninety-one patients with this lesion were treated in the Ullevaal Hospital, Oslo, in a ten-year period. Fifty-seven of these were over sixty years of age, whereas only 4 were under forty. The diagnosis was made by the characteristic symptoms and scout films of the abdomen. When there was fever and leukocytosis, the assumption of vascular disturbance led to immediate laparotomy and exteriorization of the bowel. If the patients had no signs or symptoms of necrosis, they were sigmoidoscoped and relieved by the passage of a soft-rubber rectal tube into the distended twisted segment of bowel. This method was successful in 123 cases. Recurrences accounted for the fact that the 91 patients had a total of 168 admissions to the hospital. If elective surgery was carried out, it was done in four stages, as follows: cecostomy, followed by exteriorization of the sigmoid with later operative closure, and finally closure of the cecostomy.

Guptill<sup>94</sup> has collected from the literature 347 cases of familial polyposis of the colon. He adds 5 cases occurring in two families that he has encountered. Very low ileorectal anastomosis with colectomy in stages is recommended. Polyps in the retained rectum must be treated by fulguration when they are found on regular examinations. The intervals of these inspections may vary from one to six months, depending on the rate at which new polyps develop. Guptill calls attention to the advisability of careful examination of all members of such families. Even those who do not have polyposis are prone to develop carcinoma of the colon on the basis of a single polyp.

The evolution of adenomas of the large intestine and their relation to carcinoma are discussed by

Helwig.<sup>95</sup> His report is based on 1460 consecutive autopsies in which 139 subjects, or nearly 10 per cent, had adenomas of the colon. Twelve of these revealed cancer on microscopical examination. He states that adenomas are true tumors and are not based on previous inflammation. The incidence was greater in white persons than in Negroes. Also, it was greater in men than in women. The incidence increased with age, and 24 per cent occurred in the eighth decade of life. The average number of adenomas found was two per subject, although 58 per cent revealed a single lesion.

Bartlett<sup>96</sup> reviews the results of treatment of 298 colostomies in an Army hospital center. He advises meticulous removal of all scar tissue of the skin, fat, fascia and bowel, followed by an accurate suture of the bowel, which is dropped free into the peritoneal cavity. Careful wound closure is then accomplished. There was only 1 fatal case in the 298 closures, which included 60 end-to-end anastomoses.

An ingenious and effective method of preparing the obstructed colon is reported by Millet.<sup>97</sup> A large rubber-tube cecostomy is done after a modification of Gibson's technic. Twenty-four hours later, a small opening is made into the anterior wall of the tube. Through this is passed a Miller-Abbott tube, which is carried by peristalsis gradually to the point of obstruction. Irrigation can then be successfully carried out through the long double-lumen tube. The bowel proximal to the obstruction can thus be thoroughly cleansed in four or five days.

Ochsner and Hines<sup>98</sup> analyzed the records of 113 consecutive cases of carcinoma of the colon coming under their care. Ninety-six of these patients, or 84.8 per cent, had resections as follows: 18 right colectomies, with no deaths, 56 left colectomies, with 2 deaths, and 48 rectosigmoid, usually by combined abdominoperineal operations, with 2 deaths. The resectability was highest in the rectosigmoid group. The authors stress the danger of recurrence when continuity is attempted in patients with low and extensive lesions.

Experience with cancer of the colon at the Massachusetts General Hospital has been brought up to date.<sup>99</sup> The resectability rate was 95 per cent in the last group of cases, as compared to 91 per cent in a former series. Primary anastomosis is done in all cases except those requiring combined procedures. An outer row of fine cotton and an inner row of fine catgut sutures are used in an open anastomosis. Obstructed cases have preliminary cecostomy, and if this is not effective, transverse colostomy is done. All patients are treated for from five to seven days with 8 gm of sulfathaladine daily before operation. Secondary wound closure is practiced. The mortality rate has been greatly reduced, largely owing to better preparation, anesthesia, blood replacement and antibiotics.

Johnston<sup>100</sup> has collected from the literature 48 cases of carcinoma of the colon occurring in children under sixteen years of age. He reports a case of colloid carcinoma of the right portion of the colon in a three-year-old child. He states that colloid carcinoma is ten times as frequent in children with cancer of the colon as it is in adults.

Gilchrist and David<sup>101</sup> have reviewed 200 cases of carcinoma of the colon and rectum operated on more than five years before. The operability rate for this period was 75 per cent, and the operative mortality was 9.5 per cent. One hundred and twenty-five patients had lymph-node metastasis. One hundred and fourteen patients, or 57 per cent, were alive and apparently well five or more years after operation. Eight patients died during the five-year period of causes other than recurrent cancer. Seventy-eight and five tenths per cent of the patients who survived for five years had no lymph-node involvement at the time of operation, whereas 44.8 per cent of those with lymph-node involvement lived five or more years. The survival rate was somewhat greater in the intraperitoneal than it was in the extraperitoneal lesions. The right portion of the colon was more favorable for cure than the left. In 35 patients with resectable extension of disease to other structures, 14 were alive and well five or more years after operation. In 11 autopsies done on patients failing to survive operation, residual positive lymph nodes were found in 4.

A ten year follow-up study on 337 patients with cancer of the colon and rectum has been presented by Colcock.<sup>102</sup> Of 103 cases of cancer of the colon, 81 (78.6 per cent) were resected. The operative mortality in this group was 16 per cent. The Mikulicz type of resection was generally used. Of 38 patients without lymph-node involvement, 5 died in the hospital, and 5 died of unrelated disease afterward. Of the 28 remaining in this group, 18 were well at the end of five years, 2 died of recurrence between the fifth and tenth years, and 16 were well at the end of ten years. Of patients who survived operation in this group, 64.3 per cent lived five years, and 57.1 per cent lived ten years. In 27 cases with extension of disease, 8 died after operation, 15 died of recurrence within five years, 1 died of recurrence after five years, and 3 were alive and well after ten years. The results on cancer of the rectum and rectosigmoid were better. There were 60 per cent five-year and 51.6 per cent ten-year survivals in cases considered favorable at the time of operation, although in the unfavorable group, there were 30.2 per cent five-year and 23.2 per cent ten-year respites. The report of Gilchrist and David<sup>101</sup> is on a slightly different basis, and this may account for the apparent variation in results in these two important contributions.

Mider<sup>103</sup> gives an interesting analysis of 726 cases of carcinoma of the colon in which 21 patients had

multiple carcinomas in the bowel, 17 cases being found at the first operation and 4 appearing later in life. Adenomatous polyps were found in 8 patients elsewhere in the colon but more usually near the site of the cancer. Seventeen per cent of the patients with single cancers had polyps as well, and 38 per cent of those having multiple malignant lesions had polyps elsewhere in the bowel.

Dunphy<sup>104</sup> has reported the results obtained in reoperation in 4 patients with recurrent carcinoma of the colon. These patients seemed to have local recurrence only, without evidence of extension to the liver and so forth. They enjoyed long respites after bloc excision of these recurrent lesions, which often involved neighboring but nonvital structures. In an attempt to explain the local rather than distant metastases, it appeared that these lesions were originally associated with inflammatory processes. Dunphy reasoned that the lymph channels leading from the area might have been previously blocked by inflammation, which led to the gradual development of remediable local recurrence.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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### CASE 34111

#### PRESENTATION OF CASE

**First admission** A fifty-eight-year-old man was admitted to the hospital with progressive weakness and malaise

Four months before entry he noticed weakness and fatigue, which at first he attributed to overwork. Two months later he developed a sharp pain in the right loin, which was worse on deep inspiration. This was soon followed by cough with copious yellow sputum and a temperature of 102°F. Aspirin was given, and the right side of the chest was strapped, with slight improvement. He was then given sulfadiazine for nine days, and the temperature fell to normal but rose again after the drug was stopped, fluctuating between 99 and 102°F. There were no actual chills. Two weeks before admission he experienced a sharp severe left-upper-quadrant pain, which came on suddenly and was made worse by deep inspiration. It was accompanied by nausea, vomiting and increased fever and required morphine for relief. The pain gradually subsided over several days.

A heart murmur had been discovered on routine physical examination twenty-five years previously

and had again been noted two years before entry. There was no history of rheumatic fever.

Physical examination revealed a poorly nourished man, with pale dry skin and café-au-lait spots over the abdomen and extremities and several petechiae over the anterior surfaces of the legs. There was slight ankle edema. The heart was questionably enlarged. There were harsh systolic murmurs at the apex (Grade I) and at the base (Grade III). The aortic second sound was slightly greater than the pulmonic. There were a few moist rales at the right base. The spleen was very large, 11 cm down in the nipple line, hard and moderately tender. The liver was not definitely enlarged.

The temperature was 101°F, the pulse 88, and the respirations 22. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood disclosed a red-cell count of 3,000,000, with a hemoglobin of 11 gm, and a white-cell count of 3300, with 58 per cent neutrophils and 42 per cent lymphocytes. The serum nonprotein nitrogen was 41 mg per 100 cc, the total protein 7.2 gm, and the chloride 102 milliequiv per liter. The urine was loaded with red cells. Blood cultures were negative. An x-ray film of the chest showed partial collapse of the left upper lobe, with many areas of increased density and emphysematous blebs in the left apex. There was no infiltrative lesion. The heart and great-vessel shadows were normal. A plain film of the abdomen showed proliferative changes in the lumbar spine and a soft-tissue mass in the left side of the abdomen. An electrocardiogram was within normal limits.

The patient was started on penicillin, 500,000 units daily, later increased to 1,000,000 units and then to 2,000,000 units a day. After sixteen days of this therapy he was still having a low-grade fever and had developed an area of cellulitis at the site of the eight-day intramuscular constant penicillin drip. The drug was accordingly stopped, and blood cultures were pursued with renewed vigor without

success. Two sternal-marrow aspirations were also negative on culture. He was given four transfusions of 500 cc of blood each.

One month after admission he developed diarrhea, nausea and left abdominal pain. Examination revealed slight tenderness over the spleen and a slightly high-pitched hypoactive peristalsis, and there were new petechiae over the legs. He was then put on penicillin, 10,000,000 units intramuscularly a day in 800 cc of physiologic saline solution for four weeks with no response. During that time the white-cell count was 2500 to 8000, the hemoglobin 9.5 to 13.5 gm, the serum nonprotein nitrogen 35 to 40 mg per 100 cc, the total protein 6.1 to 7.4 gm with an albumin-globulin ratio of 0.9, the carbon dioxide 24 milliequiv and the chloride 100 milliequiv per liter, the cephalin flocculation reaction was +++ in twenty-four hours. The bromsulfalein test showed 18 per cent retention of the dye in forty-five minutes. The prothrombin time was normal. Repeated blood cultures (thirty-one in all) were still negative. The blood penicillin level was between 9.14 and 0.6 units per cubic centimeter. The urine consistently showed profuse hematuria and +++ test for albumin, the specific gravity ranging from 1.005 to 1.012. The stools were negative.

Two months after admission the patient developed ascites, and the venous pressure in the right arm was equivalent to 6 cm of saline solution. Two weeks later he had tenderness in the right calf, with some enlargement of this area, but a negative Homans's sign and absence of increased heat or dilated superficial veins. On the following day he had bilateral ankle edema, nausea and vomiting, restlessness, and pain in the anterior left portion of the chest and precordium, exaggerated by respiration. The heart rate was 100 per minute, and there was a gallop rhythm. The blood pressure was 158 systolic, 108 diastolic. An electrocardiogram showed no significant change, and a chest film revealed fluid in the right base and prominent lung roots. He was then given 0.1 gm of digitalis daily, and after a week the gallop rhythm disappeared and the edema subsided. A thoracentesis yielded 575 cc of straw-colored fluid. A biopsy of the deltoid muscle showed a small focus of degeneration with lymphocytic and monocytic infiltration. A tuberculin test gave a 2-cm area of erythema in forty-eight hours. The temperature gradually became normal. The patient was discharged three months after admission.

**Final admission** (six months later). In the interval he was taking digitalis, ferrous sulfate and components of the vitamin B complex. He felt better temporarily, and the spleen decreased in size, but later the weakness and malaise increased and he had an irregular fever. Two months previous to this admission he had an attack of left-upper-quadrant pain lasting for two days. One month later the left-upper-quadrant pain came on sharply and persisted

It was made worse by respiration, by lying on the left side and on motion and palpation of the left upper quadrant. The left shoulder and right knee were occasionally painful but not red, hot or swollen. Three weeks previous to admission he stopped the digitalis, and this did not result in increased dyspnea, cyanosis or edema. However, anorexia, malaise and fatigue became prominent symptoms, along with dry mouth, constipation and drowsiness. The urine was consistently dark.

Physical examination revealed a wasted lethargic man with fetid breath. There were numerous petechiae over the forearms, abdomen and thighs. The heart was not enlarged, there were harsh systolic murmurs at the apex and base and a high-pitched diastolic murmur in the aortic area along the left sternal border transmitted over the upper anterior portion of the chest. The aortic second sound was diminished. There were slight dullness and bronchial breathing over the left upper chest. The spleen was tender and greatly enlarged, reaching almost to the pelvis. The liver was 2 cm below the rib margin and not tender. There was no dependent edema.

The temperature was 98.6°F, and the pulse 84 and regular. The blood pressure was 110 systolic, 60 diastolic.

The white-cell count was 4000, with 86 per cent neutrophils. The serum nonprotein nitrogen was 122 mg per 100 cc, and the carbon dioxide 21.4 milliequiv per liter. The urine repeatedly showed gross hematuria and albuminuria and a specific gravity ranging from 1.008 to 1.010. A chest film showed collapse of the left upper lobe as before, but there was complete disappearance of the pleural effusion. An electrocardiogram showed a partial aorticulventricular and intraventricular block. Blood cultures were negative.

The patient continued to have severe pain in the left shoulder and left upper quadrant, and he ate and drank very little. He was given fluids parenterally but no penicillin. The temperature and respiratory rate remained normal, whereas the pulse varied between 80 and 90. The nonprotein nitrogen rose progressively to 155 mg per 100 cc, and the carbon dioxide fell to 16.6 milliequiv per liter. He became disoriented and stuporous, and the skin petechiae increased in number. Finally one month after admission, the temperature, pulse and respirations increased to 100.5, 115 and 24 respectively and he died the following morning, fourteen months after the onset of the illness.

#### DIFFERENTIAL DIAGNOSIS

**DR CONGER WILLIAMS.** In summary this patient was a fifty-eight-year-old man who died of a long febrile disease, approximately 14 months after the onset of the illness. There was a marked leukopenia, only 4000 white cells per cubic centimeter, and a mild splenomegaly, only 2 cm above the costal margin.



numerous petechiae, a persistent leukopenia and hematuria. On thinking over this very complicated problem, I believe that the possible diagnoses might be grouped under three headings. The first possibility is infection, the second, neoplasia, and the third, connective-tissue disease, such as periarteritis nodosa or lupus erythematosus.

Under the heading of infection, subacute bacterial endocarditis is the best possibility. This patient had definite heart disease, with systolic and diastolic murmurs, a persistent elevation of temperature, petechiae and successive episodes of left-upper-quadrant pain, suggesting recurrent emboli to the spleen. Another feature that fits with the diagnosis of subacute bacterial endocarditis is that of hematuria. However, I believe that macroscopic hematuria occurring so consistently during the course of subacute bacterial endocarditis is unusual. I also thought that the number of petechiae in this case was unusual. Ordinarily in subacute bacterial endocarditis, occasional petechiae are seen, when they occur in large numbers the more acute bloodstream infections or blood dyscrasias must be considered in the differential diagnosis. Another point in support of the diagnosis of subacute bacterial endocarditis was the development of the diastolic murmur along the left sternal border. Erosion of the aortic valve when it is the seat of a vegetative growth often produces such a murmur in the course of the disease. However, there is one point much against the diagnosis—the report that thirty-one blood cultures were negative. It is true that occasional cases of subacute bacterial endocarditis are seen in which a great many cultures are negative, possibly because an unusual organism, which is difficult to grow, happens to be the infecting agent. I think in this case thirty-one negative cultures are a strong argument against the diagnosis. Also, but less positively, against the diagnosis of subacute bacterial endocarditis is the lack of response to penicillin. This patient was given as much as 10,000,000 units a day over a period of one month. This does not rule out subacute bacterial endocarditis, but it does incline one a little bit against the diagnosis, especially in the absence of positive cultures.

No other diagnosis need be considered seriously under the heading of infections. Tuberculosis is a possibility in view of the long history of fluctuating temperature and the splenic enlargement and possibly the urinary findings. There was also a positive tuberculin test. However, I believed that the diagnosis of tuberculosis was very unlikely.

I think it might be a good plan to look at the x-ray films at this point.

DR. STANLEY M. WYMAN: The films show that the heart is enlarged without any particularly characteristic configuration. The collapse of the left upper lobe is seen at the left apex, but the outline is imperfectly visualized in the lateral view. The film taken to show the bronchi is not satisfactory. There

seems to be no definite obstruction in the bronchus itself. There is some calcification suggesting that the process is very old. The lung fields otherwise are clear. The film taken three weeks after this first film shows a considerable amount of fluid in the right side of the chest and to a lesser extent in the left. There is hazy density throughout the medial portions of the lung field spreading out from the hilum. This cleared completely as is seen on the film taken several months later.

A pyelogram was done. The kidney shadows are of normal contour and size and show no evidence of calcification. The enlarged spleen is very easily seen lying almost at the level of the iliac crest. The dye was excreted in poor concentration by both kidneys after considerable delay, but the outline of the urinary passages is not sufficiently satisfactory to detect any but the grossest disease. I can see no definite abnormality. There is certainly nothing to suggest an active tuberculous lesion in the lung.

DR. WILLIAMS: What about malignant tumors? Lymphoma is always a possibility when one is dealing with widespread systemic disease of this kind, and certainly it is capable of producing a persistent rise in temperature over a period of many months. Another thing that suggests the possibility is the fact that the leukopenia was rather marked and persistent. In lymphoma it is possible to have invasion of the bone marrow, with persistent leukopenia. Leukopenia, of course, is often the rule in subacute bacterial endocarditis, but it seems to me that the white-cell count was quite low, going as low as 3000 and even lower at times. Other points that suggest the possibility of lymphoma are the very persistent hematuria and albuminuria, indicating involvement of the renal tissues by a malignant process. As I said before, it is possible for the embolic phenomena in subacute bacterial endocarditis to produce this picture, but the amount and persistence of hematuria were a little bit unusual for that.

If one makes a diagnosis of malignant tumor, some of the clinical findings must be explained by assuming the presence of other disease. It seemed to me fairly definite that this patient had congestive heart failure at one time. This might be explained on the basis of long-standing aortic stenosis. Active rheumatic fever is another possibility, especially if the valvular lesions were the result of previous rheumatic infections. Recurrence of rheumatic fever is not uncommon during the course of subacute bacterial endocarditis. The possibility of myocardial involvement with a tumor process is remote. Mention was made at one point of the electrocardiographic finding of partial heart block and intraventricular block. Partial heart block is consistent with active rheumatic infection but also consistent with many other destructive lesions in the heart, as well as with coronary disease.

Metastatic carcinoma is a possibility, but I cannot imagine where the primary site would have been.

Another diagnosis to be considered is one of the "group" diseases. The possibility of periarteritis nodosa might explain the hematuria and albuminuria. The patient had a course of sulfadiazine earlier in the disease. It is well known that periarteritis nodosa may occur as a sensitivity reaction to sulfonamides, but that again is very remote. The possibility of lupus erythematosus always comes up but can hardly merit serious consideration here. I am left with two possibilities to explain the symptoms: rheumatic heart disease, with subacute bacterial endocarditis, and rheumatic heart disease with lymphoma. The thing that makes it difficult to accept subacute bacterial endocarditis is the large number of negative blood cultures, although almost everything in the history and findings suggests the diagnosis. I am inclined to accept the diagnosis of lymphoma.

DR. BENJAMIN CASTLEMAN: How do you account for the change in the murmur of a straight rheumatic basis?

DR. WILLIAMS: If the patient had active rheumatic infection he might well have had changing murmurs, especially if the infection were present over a long period. Also, a diastolic murmur could have been present before but might not have been heard.

DR. EDWARD F. BLAND: This case puzzled us for fourteen months. We went through the same line of reasoning. The fact that we were willing to treat the patient with 10,000,000 units of penicillin intramuscularly per day is an indication that we believed strongly in the diagnosis of subacute bacterial endocarditis.\* The statement in the record that he had thirty-one negative blood cultures is a modest one, because he actually had a good many more. During the second admission the whole problem was one of uremia. He was totally afebrile, and the pulse was quiet. Further blood cultures up to the time of death were negative. Actually, he died in uremia, without fever or evidence of sepsis. The hematuria continued to the end. The systolic murmur dated back many years. He had no definite rheumatic fever, and because the physical signs were those of aortic stenosis, presumably since youth, we thought of the possibility of a calcified bicuspid valve.

DR. WILLIAMS: Is it not unusual for a murmur heard twenty-five years previously to be based on a bicuspid valve? Of course another murmur, a functional murmur, may have been heard twenty-five years before.

DR. WALTER BAUER: I saw many such cases in the service.

DR. WILLIAMS: I believe that the murmurs are heard as they become more calcified in later years.

DR. BLAND: When we see frank aortic stenosis in patients under the age of twenty, we believe that a considerable number have a bicuspid valve secondarily scarred by rheumatic fever.

DR. BAUER: I thought that the diagnosis was subacute bacterial endocarditis. However, I did suggest the possibility of bistoplasmosis or toxoplasmosis but not seriously.

#### CLINICAL DIAGNOSIS

Subacute bacterial endocarditis

#### DR. WILLIAMS'S DIAGNOSES

Rheumatic heart disease, with aortic stenosis and regurgitation  
Lymphoma

#### ANATOMICAL DIAGNOSES

Subacute bacterial endocarditis  
Congenital bicuspid aortic valve  
Bronchopneumonia  
Subacute glomerulonephritis  
Healed pulmonary tuberculosis  
Infarcts of the spleen, multiple

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: We have a photograph of the heart, which was slightly enlarged and showed a bicuspid aortic valve (Fig. 1). The valve flaps were covered with warty vegetations, and at one point there was a perforation through the cusp. A blood culture taken at the time of post-mortem examination was negative. However, in cultures made directly from the vegetations, alpha-hemolytic streptococcus grew out. When the organism was tested for penicillin sensitivity it was found to be extremely resistant, being inhibited only at 5 units per cubic centimeter, the highest dosage in which we tested it. The other point of major interest was the kidneys, which weighed 250 gm., were small for a man and showed scattered petechiae over the surface. Microscopical sections did not particularly suggest the focal or embolic type of nephritis usually seen in subacute bacterial endocarditis. I would classify the lesion as subacute or early chronic diffuse glomerulonephritis, which is also sometimes seen with bacterial endocarditis.

Microscopical sections of the heart valves showed extensive calcification of the vegetations, but foci of activity were still present. One rather unusual feature that I cannot remember ever having seen before was a small island of cartilage formation in one of the cusps. One sometimes sees metaplastic bone formation, but I do not happen to have seen metaplastic cartilage before in a heart valve.

The spleen weighed 650 gm. and showed three separate old infarcts. There were widespread petechiae throughout the body, skin and mucous membranes. There were a number of spots of fibrosis and one spot of fresh local infarction in the myocardium itself—unquestionably the result of very

\*This large dosage of penicillin was made possible through the courtesy of the Lederle Laboratories, New York City.

small emboli in the coronary system At the time of death the patient also had an extensive bronchopneumonia

DR BAUER At the time of autopsy was the lung consolidated?

DR MALLORY There was an old emphysema and fibrosis but no evidence of active tuberculosis

DR BAUER Was there any evidence of bronchial disease?

DR MALLORY No

DR BLAND This case illustrates one of the first patients that we have had the courage to treat so vigorously on suspicion alone In looking back, we were right, but perhaps we did not go far enough



FIGURE 1

The case illustrates the fact that older people with bacterial endocarditis are apt to run a milder course and that the disease is consequently more difficult to recognize Of course, it is easy now, but in retrospect we thought that we had controlled the disease since the patient was better when he went home after the first admission I would like to ask Dr Bauer if he thinks we should have been even more courageous and given streptomycin We were afraid of sulfadiazine because of the renal situation and because he was bordering on uremia even at the first admission

DR BAUER In retrospect, yes At the time I saw the patient I was opposed to continuing treatment because I did not believe that penicillin would be effective I had no right to make that statement because we did not know the causative organism or its penicillin sensitivity

## CASE 34112

### PRESENTATION OF CASE

*First admission* An eighty-nine-year-old woman was first admitted to the hospital with a five-day history of constipation and gradually increasing distention

The patient had been perfectly well until admission and had normal bowel habits There was no history of melena

Physical examination showed a well preserved woman in no discomfort There was marked kyphoscoliosis to the right The heart sounds were snapping, and there was a soft apical systolic murmur The abdomen was distended, tense and tympanitic, with rushed normal-pitched peristalsis in the left lower quadrant On rectal examination at the end of the finger was an irregular mass almost encircling the rectum, which felt as though it lay outside the mucosa This was nontender, and there was no blood on the examining finger

The temperature, pulse and respirations were normal

A temporary cecostomy was done the next day A week later a sigmoidoscopy was done, which showed no intrinsic tumor tissue, and a permanent double-barreled colostomy was made At this operation the surgeon noted an area of diverticulosis of the sigmoid about 10 cm long at the end of which was a tight constriction There was no involvement of the peritoneum by tumor The patient was discharged two months later

*Second admission* (five years later) In the interval she had been in fairly good health She had severe rectal tenesmus occurring in spasms several times a day, with the passage of moderate amounts of mucus and blood at times during the past year A year before readmission she passed a mass the size and shape of a duck's egg This was made up of inspissated mucus with no blood Six months later she entered another hospital complaining of chills, fever and low abdominal tenderness, but this cleared up with sulfadiazine At that time and on numerous other occasions, rectal examination showed a narrowing of the rectum, beginning 10 cm from the anus, with a large mass about it and filling the pelvis Three days before readmission she began to have severe chills and fever and lower abdominal pain On the day of admission there was abdominal distention and passage of nothing by colostomy

Physical examination revealed slight tenderness in the lower abdomen and normal-sounding peristalsis The blood pressure was 100 systolic, 60 diastolic A rectal examination was reported as follows "At one finger's length inside the anus is a large, hard, tender, slightly movable mass with a central small lumen that admits the tip of the finger There is blood on the rectal glove"

The white-cell count was 30,000, with 90 per cent neutrophils The hemoglobin was 9.7 gm, and the serum nonprotein nitrogen was 42 mg per 100 cc The urine contained albumin and many pus cells

A plain film of the abdomen showed numerous dilated loops of small and large bowel, with no gas in the distal sigmoid

A colostomy irrigation resulted in the passage of much gas

The patient was given penicillin and streptomycin but continued to have a low-grade fever, the temperature ranging from 99 to 101°F, with occasional elevations to as high as 103°F. The pulse varied from 80 to 100, and the respirations from 20 to 30. Repeated laboratory studies continued to show leukocytosis, albuminuria and pyuria. There was a rectal discharge, and irrigations yielded dark-green mucoid material. Finally she had great urinary frequency and was placed on constant bladder drainage. She died eight weeks after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. JOSEPH A. HOLMES: Although it is fairly evident that this patient's two admissions were related, and it may be shown that there was only one lesion responsible for the illness at both admissions, I shall discuss each admission separately.

We have a very short and meager history of the illness prior to the first admission. Two pertinent statements were made, however — that she had been well, with normal bowel movements, and that there was no history of melena. A five-day history of constipation and gradually increasing distention leads one immediately to the assumption that there was probably frank obstruction, primarily in the large bowel, especially in the absence of any note regarding cramps, pain or vomiting.

On physical examination the findings were quite remarkable for a woman of eighty-nine years. Small-bowel obstruction appears to have been ruled out by the presence of normal-pitched peristalsis and by the absence of elevation of pulse, temperature and respirations. On rectal examination a mass was noted, although the examiner appears to be quite definite in the statement that the mass lay outside the rectal mucosa. No blood was noted on the examining finger.

We have no laboratory data on the first admission, nor is any statement made of a plain film of the abdomen. I doubt that such information would be of any assistance other than to confirm our impression that she had an acute obstruction. There is no mention of the passage of gas by rectum, so I shall assume that there was none and that there was sufficient evidence of large-bowel obstruction so that a cecostomy was done the following day. The decompression apparently relieved her sufficiently so that a week later the exploration of the abdomen could be carried out. At operation an area of diverticulosis of the sigmoid was noted, and at the lower end of this area a tight constriction was found. There was no involvement of the peritoneum or of the perirectal tissue by tumor, and no tissue was removed for biopsy.

I believe that the discussion of such cases as this at these conferences has emphasized the frequency with which carcinoma is associated with diverticulitis of the sigmoid colon. No intrinsic tumor tissue was noted on sigmoidoscopic examination, and I am

totally in agreement with the operator that in such circumstances one must assume that the entire lesion is on the basis of diverticulosis, with an area of diverticulitis at the lower end. It is probably next to impossible at operation to distinguish frank cancer associated with diverticulitis from a cicatrizing inflammatory process. I am emphasizing this because of the importance that is attached to the sigmoidoscopic examination as a preoperative procedure.

There are numerous factors involved in this case, and it is for those managing the case at the time to make the decision. Certainly the patient had lived beyond the average life span, and we know little enough about her nutrition and general condition to encourage a more radical procedure than was carried out. A permanent double-barreled colostomy was done, and she was discharged two months later.

Turning now to the second admission, five years later, we find that she had been well over this period except that she had had severe rectal tenesmus and had passed moderate amounts of mucus and blood at various times during the past year. It is obvious that there was a progressive change in the local lesion in the rectum. There was definite involvement of the mucosa, and the lumen had become smaller. There was also evidence of an inflammatory process in that she was running a low-grade fever, with occasional temperature elevations to 103°F and an elevation in the white-cell count. A fairly marked anemia was present.

Much of the evidence presented in this case leads one to believe that the lesion noted at the original operation, which persisted to death, might possibly have been that of an annular carcinoma. However, from the various studies of untreated cases of carcinoma of the colon, the life expectancy in these cases at best is not over twenty months. In the cases reported by Nathanson and Welch\* the expectancy was only fourteen months. It is necessary, then, to consider other possibilities.

Tuberculosis of the rectum is such a rare disease that I feel justified in dismissing it, particularly on the basis of the findings at the original laparotomy.

Other granulomatous lesions should be considered. Actinomycosis is a very rare disease, and such a lesion present for five years, I believe, would have caused fistulas either above or below.

There remain then few other possibilities. Malignant melanoma of the bowel, although rare, occurs frequently enough to be seriously considered in any age group. I wanted to make that diagnosis in this case, believing that the mention of the dark-green material returned with the rectal irrigations might be a clue to the nature of the lesion. This sort of material is not typical of melanoma. Again, a melanoma of the rectum would have been detected either

\*Nathanson, I. T., and Welch, C. L.: Life expectancy and incidence of malignant disease III. Carcinoma of gastro-intestinal tract. *Am. J. Cancer* 31:457-466, 1937.

on sigmoidoscopic examination or by the appearance of the bowel at the time of operation. Also, a melanoma is usually a rapidly growing lesion and if present for five years should, I believe, have become quite distinctly larger locally, with evidence of wide spread to other tissues such as the liver. No mention is made of an enlarged liver. On a similar basis, I shall exclude lymphoma of the bowel, for I believe that the lesion existed too long to have confined itself to the original locale.

This leaves me but one choice — an inflammatory process, which could well have occurred on the basis of diverticulitis alone or on the basis of diverticulosis and the presence of a foreign body that had become lodged in the area of constriction, with the subsequent development of a pelvic abscess, which gradually increased in size. We know that she had diverticulosis at the time of the first admission, and we know that diverticulitis can produce the narrowing described. I believe that the duration of the lesion over a five-year period is in favor of that diagnosis, as is the description of the terminal illness. The increased size of the local lesion can be accounted for by the formation of an abscess about it, even though the bowel had been nonfunctioning. I believe that the evidence points more toward this, with the spread of the infection eventually to involve the small intestine, causing partial obstruction to the small bowel. My diagnosis, then, remains as diverticulitis as the primary disease, with terminal abscess formation and small-bowel obstruction.

DR ERNEST M. DALAND: I first saw this patient at her home in the middle of the night. I brought her to the hospital and did a cecostomy under novocain at once. No x-ray studies were made before the second operation. The point of obstruction was obvious — high in the rectum. No tissue for biopsy could be obtained on proctoscopic examination. Only the ampulla could be inspected by the proctoscope, since obstruction was complete.

Before the exploratory operation my diagnosis was carcinoma. Afterward, because of the area of diverticulosis visualized, I believed that there was a chance that the entire process was diverticulitis. I raised the question of cancer. I told the family that I could not tell which it was but that time alone would tell.

As each of the five years passed until the next hospital admission, with very little change in the ex-

aminations, it seemed probable that the disease was diverticulitis and not cancer. During the final illness the presence of pus in the urine, the bladder irritability, the fever and the high white-cell count made me believe that the patient had a pelvic abscess from the diverticulitis and that she probably had a bladder fistula. No attempt was made to prove this, for it was believed that the treatment already instituted would not be changed.

#### CLINICAL DIAGNOSIS

Diverticulitis of sigmoid, with pelvic abscess and fistula into bladder

#### DR HOLMES'S DIAGNOSIS

Diverticulitis of sigmoid, with pelvic abscess

#### ANATOMICAL DIAGNOSES

*Adenocarcinoma of rectosigmoid (Grade II), with secondary abscess formation and extension into pelvis and uterus*

Pyometrium

Pyelonephritis, acute and chronic, left

Diverticulosis of sigmoid

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: At autopsy most of the pelvis was replaced by necrotic, friable, pale-yellow tumor, which had broken down in many areas to form green purulent abscesses. The tumor originated in the rectosigmoid and was about 8 cm long and completely annular. It had infiltrated both sides of the pelvis and extended into the uterus at the internal os to produce a pyometrium. The left ureter was surrounded by tumor in the pelvis and led to a mild pyelonephritis. Above the tumor the sigmoid contained many diverticula, but there was no evidence of infection within or around them.

The rectosigmoid tumor was a well differentiated adenocarcinoma, and I believe it might well have been present at the first operation five years before death. Tumors in elderly persons are very apt to grow slowly, invade only locally and not metastasize. Although one cannot absolutely rule out the development of the cancer on the basis of a pre-existing diverticulitis, I am more in favor of its having been present at the original admission.

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## THE BOSTON HEALTH LEAGUE

UNTIL 1948 the Boston Health League had not published a report since 1940. The current report, therefore, covers considerable ground, accounting for the League's activities both during the war and in the post-war period, from 1941 to 1947.

In March, 1941, the League formed the sub-committee on health of the Committee on Public Safety to co-ordinate the city's health activities with the general defense plan. After Pearl Harbor the Health League and the Hospital Council of Boston participated actively in the Health Services Division of the Committee on Public Safety, the executive secretary of the League and the Hospital Council acting as secretary of the Division.

A committee of the League in 1940 reviewed the mental-hygiene situation in Boston agencies to bring

up to date a decade's progress since the last previous survey. In 1943 a joint committee of the Massachusetts Society for Mental Hygiene and the Health League was formed to consider mental-hygiene problems aggravated by the war situation.

In 1941 a committee was appointed to reappraise nutrition work in Boston. In 1945, at the request of the First Service Command and the First Naval District a committee on venereal disease was organized. As a result of the activities of this committee the reporting of cases of venereal disease showed a marked improvement.

Many of the regular activities of the League were maintained during the war years. It continued its work on the Group Budget Committee on Health of the Greater Boston Community Fund. It co-operated actively with the School Committee of Boston in the establishment of a unified school lunch program, under the administration of a qualified director.

In 1943 the Boston Council of Social Agencies was reorganized and became the Greater Boston Community Council. In the following spring the Boston Health League joined it, maintaining its identity, however, within the Health and Hospital Division. This has made it inevitable that metropolitan problems should come under the scrutiny of the League, although its concern remains primarily with municipal Boston.

A review of the structure and the activities of the Health League accordingly seemed indicated, and this was made in 1947. As a result of this study it seemed wise that the structure of the League should be truly representative, with a membership composed of all important agencies, voluntary and official, working in the health field, and with integration with the Hospital and Nursing Council and the Medical Social Work group.

At the annual meeting in March, 1947, member agencies agreed that the League should stand ready to point out needs in the health field, to define, allowing for flexibility, the fields of responsibility of official and voluntary agencies to carry out, in co-operation with the Research Bureau of the Community Council studies to develop new standards and techniques and to evaluate present programs.

on sigmoidoscopic examination or by the appearance of the bowel at the time of operation. Also, a melanoma is usually a rapidly growing lesion and if present for five years should, I believe, have become quite distinctly larger locally, with evidence of wide spread to other tissues such as the liver. No mention is made of an enlarged liver. On a similar basis, I shall exclude lymphoma of the bowel, for I believe that the lesion existed too long to have confined itself to the original locale.

This leaves me but one choice — an inflammatory process, which could well have occurred on the basis of diverticulitis alone or on the basis of diverticulosis and the presence of a foreign body that had become lodged in the area of constriction, with the subsequent development of a pelvic abscess, which gradually increased in size. We know that she had diverticulosis at the time of the first admission, and we know that diverticulitis can produce the narrowing described. I believe that the duration of the lesion over a five-year period is in favor of that diagnosis, as is the description of the terminal illness. The increased size of the local lesion can be accounted for by the formation of an abscess about it, even though the bowel had been nonfunctioning. I believe that the evidence points more toward this, with the spread of the infection eventually to involve the small intestine, causing partial obstruction to the small bowel. My diagnosis, then, remains as diverticulitis as the primary disease, with terminal abscess formation and small-bowel obstruction.

DR ERNEST M DALAND: I first saw this patient at her home in the middle of the night. I brought her to the hospital and did a cecostomy under novocain at once. No x-ray studies were made before the second operation. The point of obstruction was obvious — high in the rectum. No tissue for biopsy could be obtained on proctoscopic examination. Only the ampulla could be inspected by the proctoscope, since obstruction was complete.

Before the exploratory operation my diagnosis was carcinoma. Afterward, because of the area of diverticulosis visualized, I believed that there was a chance that the entire process was diverticulitis. I raised the question of cancer. I told the family that I could not tell which it was but that time alone would tell.

As each of the five years passed until the next hospital admission, with very little change in the ex-

aminations, it seemed probable that the disease was diverticulitis and not cancer. During the final illness the presence of pus in the urine, the bladder irritability, the fever and the high white-cell count made me believe that the patient had a pelvic abscess from the diverticulitis and that she probably had a bladder fistula. No attempt was made to prove this, for it was believed that the treatment already instituted would not be changed.

#### CLINICAL DIAGNOSIS

Diverticulitis of sigmoid, with pelvic abscess and fistula into bladder

#### DR HOLMES'S DIAGNOSIS

Diverticulitis of sigmoid, with pelvic abscess

#### ANATOMICAL DIAGNOSES

*Adenocarcinoma of rectosigmoid (Grade II), with secondary abscess formation and extension into pelvis and uterus*

Pyometrium

Pyelonephritis, acute and chronic, left

Diverticulosis of sigmoid

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: At autopsy most of the pelvis was replaced by necrotic, friable, pale-yellow tumor, which had broken down in many areas to form green purulent abscesses. The tumor originated in the rectosigmoid and was about 8 cm long and completely annular. It had infiltrated both sides of the pelvis and extended into the uterus at the internal os to produce a pyometrium. The left ureter was surrounded by tumor in the pelvis and led to a mild pyelonephritis. Above the tumor the sigmoid contained many diverticula, but there was no evidence of infection within or around them.

The rectosigmoid tumor was a well differentiated adenocarcinoma, and I believe it might well have been present at the first operation five years before death. Tumors in elderly persons are very apt to grow slowly, invade only locally and not metastasize. Although one cannot absolutely rule out the development of the cancer on the basis of a pre-existing diverticulitis, I am more in favor of its having been present at the original admission.

sometimes have seemed, moving in grim majesty through the brick corridors of her hospital, those who knew her, knew her as a friend. She has left a deep imprint on the teaching of the art of nursing. That imprint bears the mark of unselfish devotion to a high calling, of practical idealism and of unflinching integrity.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**DODD** — Isaac S. F. Dodd, M.D. of Pittsfield, died on January 29. He was in his eightieth year.  
Dr. Dodd received his degree from New York University Medical College in 1890. He was a former president of the Berkshire District Medical Society, a former vice president of the Massachusetts Medical Society and a former supervising censor. He was formerly chief of staff, House of Mercy Hospital, and was a fellow of the American College of Surgeons and American Medical Association.  
His widow, a son and a daughter survive.

**HOBERMAN** — Samuel Hoberman, M.D. of Malden died on February 18. He was in his sixty-sixth year.  
Dr. Hoberman received his degree from George Washington University School of Medicine in 1907. He was physician-in-charge at the Malden Hospital for twenty-five years and was a fellow of the American Medical Association.  
His widow, three daughters and a son survive.

**O'BRIEN** — Edward J. O'Brien, M.D. of Boston, died on February 16. He was in his sixty-first year.  
Dr. O'Brien received his degree from Tufts College Medical School in 1912. He was surgeon-in-chief at the Cambridge City Hospital, consultant to Metropolitan State Hospital, Waltham, Boston State Hospital, Somerville, Choate Memorial Hospital, Woburn, and Winchester Hospital and a gynecologist at St. Elizabeth's Hospital, Brighton, for nearly thirty years. He was a member of the New England Obstetrical and Gynecological Society and the American Urological Association and a fellow of the American College of Surgeons and the American Medical Association.  
Four sons and a daughter survive.

**OSBORNE** — Carver H. Osborne, M.D. of Brookline, died on January 3. He was in his fifty-first year.  
Dr. Osborne received his degree from Boston University School of Medicine in 1921. He was formerly a member of the staff of Truist Hospital in Fall River. He was a fellow of the American Medical Association.  
His widow and a sister survive.

**REIS** — Frederick Reis, M.D. of Jamaica Plain died on February 4. He was in his seventy-second year.  
Dr. Reis received his degree from Tufts College Medical School in 1903. He was professor of physiology and biochemistry at Tufts College Medical School. He was a member of the Massachusetts Medico-Legal Society and the American Chemical Society.  
His widow survives.

**SMITH** — Frederick G. Smith, M.D. of Somerville, died on January 9. He was in his eighty-first year.  
Dr. Smith received his degree from University of Michigan Medical School in 1893. He was a member of the staff of Somerville Hospital where he was formerly chairman of the medical board. He was a former counselor of the Massachusetts Medical Society and was a fellow of the American Medical Association.  
His widow, a daughter and a son survive.

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Charles G. Shedd, *Secretary*  
422 Beacon Street, Boston

## WORCESTER DISTRICT

- BACASTOW, MERLE S., Belmont Hospital, Worcester  
University of Pennsylvania School of Medicine, 1943
- BIFIL, HORACE S., 4 Creeper Hill Road, North Grafton  
Tufts College Medical School, 1943
- CLIFFORD, WILLIAM P. J., 51 Exchange Street, Milford  
Boston University School of Medicine, 1942
- DYKENS, JAMES W., 3 Gilman Street, Worcester  
University of Vermont College of Medicine, 1945
- GREEN, ROSS W., Memorial Hospital, Worcester  
Tufts College Medical School, 1943
- HARRIS, SIDNEY, 84 Commodore Road, Worcester  
New York University College of Medicine, 1934
- HURLEY, JOSEPH P., 26 Monroe Avenue, Worcester  
Tufts College Medical School, 1940

Julius J. Tegelberg, *Secretary*  
390 Main Street, Worcester

## WORCESTER NORTH DISTRICT

- ALEXANDER, DANIEL D., Gardner State Hospital, East  
Gardner  
Middlesex University School of Medicine, 1942 Sponsor  
Charles E. Thompson, Gardner State Hospital, East  
Gardner
- COLLINGS, ROBERT Z., JR., Town Farm Road West, West  
minster  
University of Chicago, The School of Medicine, 1939
- CRUDIN, MYRTLE B., Baldwinville Hospital, Baldwinville  
Marquette University School of Medicine, 1930
- GOLDMAN, SIDNEY, 79 Prichard Street, Fitchburg  
Middlesex University School of Medicine, 1941 Sponsor  
John J. Curley, 82 Main Street, Leominster
- SIMON, AARON I., 41 Boutelle Street, Leominster  
Ohio State University College of Medicine, 1940

James G. Simmons, *Secretary*  
30 Myrtle Avenue, Fitchburg

MASSACHUSETTS DEPARTMENT  
OF PUBLIC HEALTHTRANSFER OF MASSACHUSETTS BLOOD  
PROGRAM TO AMERICAN RED CROSS

Since the American National Red Cross has committed itself to providing free blood and blood products to all the people of this country, the Massachusetts Department of Public Health will relinquish its blood-program activities to the Red Cross as part of the established nationwide program.

Arrangements are already underway whereby the Red Cross will gradually assume the blood-program responsibilities now carried by the Massachusetts Department of Public Health. Thus, there will be no interruption in the operation of the program. The Red Cross will take over the project on or be-

fore June 30, therefore, no funds are being provided in the budget of the Department of Public Health after that date for the collection, processing or distribution of whole blood.

The transfer of the blood program from the Department of Public Health to the American National Red Cross has the approval of the Massachusetts Medical Society, as evidenced by the following motion passed at a recent meeting of the Council:

that the Council of the Massachusetts Medical Society approve in principle the transfer of the Program for the distribution of Whole Blood and Blood Fractions from the Massachusetts Department of Public Health to the American National Red Cross with the understanding that this Society and the Massachusetts Department of Public Health will serve in an advisory and consultative capacity to the American National Red Cross on this Program.

The statewide blood program in Massachusetts has entered its third year. A summary of the activities of the program shows that 318 visits have been made to communities throughout Massachusetts. Since many of the clinics ran for more than one day, the mobile units actually collected blood on four hundred and sixty-nine days.

As of January 31, 1948, blood donations to the program amounted to 30,796 pints. It is interesting that more than a third of this blood was collected during the past six months. Factors contributing to this increase in donations are the intensified publicity campaigns, the addition of a second mobile unit and especially the growing consciousness on the part of the general public of the value of such an organized program.

The blood program has already saved Massachusetts residents thousands of dollars annually by providing blood and blood products free of charge. During the last three months of 1947, an average of over 1600 pints of whole blood was distributed per month, saving patients over \$40,000 a month for needed whole blood. In January, nearly 3000 units of gamma globulin, used for the modification of measles, was distributed to physicians in the Commonwealth. Commercially, this quantity of gamma globulin would have cost approximately \$18,000. It is estimated that the blood and blood products now available or being processed for distribution are valued at nearly half a million dollars.

The Blood Processing Laboratory of the Massachusetts Department of Public Health will continue to function as a fractionation plant. Research will be carried on to improve and develop fractionation methods. Studies in progress have already revealed several interesting discoveries. It has been found that outdated plasma can be used in the preparation of acceptable albumin and gamma globulin. Both these fractions made from overage blood plasma have successfully passed laboratory tests, and albumin has already proved thoroughly satisfactory after trial injections into human beings.

More than 21,000 pints of blood was donated to the blood program last year. This amount of blood is only a small fraction of the whole-blood needs of the Commonwealth. To meet this great demand it is necessary for all residents in communities throughout Massachusetts to participate in and support the vital program that will be operated by the American National Red Cross.

## BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Studies on the Influenza A Epidemic of January-March 1941 at Gningen (Holland)*. By J. A. R. Van Bruggen, M.D., L. J. Hulmer, M.D., W. A. Hoek, J. Mulder, M.D., and L. J. Zielstra. 8 paper 79 pp. with 26 illustrations. Verhandelungen Van Het Instituut Voor Preventieve Geneeskunde VII. Leiden: Stenfert Kroese 1947. \$2.00.

In this volume of proceedings the results of a study by a group of scientists on a short term intensive epidemic of influenza A are recorded. There was a total of 117 cases of which 44 were selected for research. Thirty five of these cases were identified as influenza A virus infections by ferret inoculation and by mouse protection and complement fixation tests with patient serum. Three ferret strains were adapted to mice. These strains showed no differences in antigenic structure, but they were different from the WVS strain. Clinically severe hyperemia with small vesicles of the anterior palatal pharyngeal arches seemed to be a reliable diagnostic symptom in most cases. The authors believe that in cases of suspected influenza penicillin and the sulfonamides should be used as a prophylactic measure. During periods of malignant pandemic or interepidemic influenza large stocks of these remedies should be established in every country for the purpose of preventing pneumonia especially staphylococcal pneumonia. The report discusses the epidemiology of the Groningen outbreak and presents a clinical survey of uncomplicated cases, bacterial complications of the respiratory tract including acute tonsillitis in confirmed cases of influenza viremia and immunity reactions, the treatment and prophylaxis of bacterial lung complications. It concludes with a series of case reports, a summary and a list of references. The introduction discusses pandemic and interepidemic outbreaks and provides a list of all such epidemics in the world for the period 1933-1946. The illustrations are excellent. The lack of an index detracts from the usability of the work. The publishing is good. This monograph is recommended for all medical libraries.

*Catalogue of the Mutter Museum of the College of Physicians of Philadelphia Part I*. Compiled by Ella N. Wade. Curator. 4 paper 89 pp. Philadelphia: College of Physicians 1947.

In 1863 Dr. Thomas D. Mutter presented to the College of Physicians of Philadelphia his museum of normal and pathologic specimens. The collection was merged with one already in the possession of the College. The specimens today number over seventy three hundred and the only catalog available has been a typewritten copy in three volumes. In 1946 the idea of publishing a catalog was inaugurated and a general plan formulated and after some regrouping of specimens this first part of the projected catalog was published in the *Transactions of the College*. Further installments will be published from time to time until the work is completed. The final installment will comprise a list of donors and an index. The College is congratulated upon making available a catalog of this fine collection.

*Problems of Early Infancy* (Transactions of the First Conference March 3-4, 1947, New York City) Edited by Milton J. E. Senn, Department of Pediatrics, Cornell University Medical College 8°, paper, 70 pp New York Josiah Macy, Jr., Foundation, 1947 75¢

In this small volume the various papers read at the first conference on the problems of infancy are presented. Fourteen papers were read by psychiatrists, psychologists, social workers, pediatricians and obstetricians. The primary themes discussed were the importance of breast feeding and the rooming-in project, whereby the mother and newborn infant are kept together in one room, instead of being separated, and whereby the mother cares for her child so far as possible.

*Spezifische Typhustherapie mit einem Beitrag zur Typhuspathogenese* Von Dozent Dr. Ferdinand Nagl und Dr. Oskar Lachner 8°, paper, 63 pp, with 32 illustrations Wien Verlag Wilhelm Maudrich, 1947

This monograph discusses the vaccine treatment of typhoid fever and is based on the authors' experience in the Floridsdorf Hospital in Vienna during 1945-1946. The total admissions were 359. Various methods of treatment were used for 272 cases, and vaccine therapy for 87 cases. The total mortality was 16.4 per cent (45 cases), but only 1 patient treated with vaccine died. The material is well organized and discusses allergy and immunity, pathogenesis, bacillemia, pathological anatomy, method of vaccine therapy, statistics and the clinical aspects, illustrated with a number of temperature charts. The paper, type and printing are excellent.

## NOTICES

### GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, March 16, at 8:15 p.m. A symposium on thoracic surgery will be presented.

#### PROGRAM

Surgical Treatment of Carcinoma of the Esophagus Dr. Richard H. Sweet  
Surgical Aspects of Pulmonary Disease Dr. John W. Strieder  
A Survey of Current Heart Surgery Dr. Dwight E. Harken

### NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Tuesday, March 23, at 8 p.m.

A business meeting consisting of reading of minutes of the previous meeting, reports of committees, communications and new business will be held.

A scientific program entitled "Harvard Night" will be presented.

#### PROGRAM

Harvard Medical School Present and future plans  
C. Sidney Burwell, M.D.  
Acute Blood Dyscrasias  
Thomas H. Ham, M.D.  
Replacement Therapy in Gastrointestinal Emergencies  
Chester M. Jones, M.D.  
Certain Cardiac Emergencies  
Samuel A. Levine, M.D.  
Surgical Treatment for Coarctation of the Aorta  
Robert E. Gross, M.D.

### HARVARD SCHOOL OF PUBLIC HEALTH

The Harvard School of Public Health announces that the Cutter Lecture on Preventive Medicine, initiated in 1912, will be held in the amphitheater of Building D, Harvard Medical School, on Monday, April 12, at 5 p.m. Dr. William N. Pildes, medical officer of health, Aygarth Rural District, Yorkshire, England, will speak on "Epidemiology in Country Practice."

The medical profession, medical and public-health students and others interested are cordially invited to attend.

## AMERICAN SOCIETY FOR THE STUDY OF STERILITY

The fourth annual national session of the American Society for the Study of Sterility will be held at the Congress Hotel, Chicago, on June 21 and 22. The two-day program will be divided into a special series of panel discussions on male infertility, with papers on female infertility and miscellaneous aspects on the second day.

The chairman is Professor Edwin G. Robertson, chairman, Department of Obstetrics and Gynecology, Queens University Faculty of Medicine, Ontario, Canada.

Additional information may be obtained from the secretary, Dr. John O. Haman, 490 Post Street, San Francisco 2, California.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 18

#### THURSDAY, MARCH 18

12:00 m. Medical Staff Meeting Nurses Home Allerton Hospital, Brookline

#### FRIDAY, MARCH 19

\*9:00-10:00 a.m. Some Aspects of Auscultation of the Heart Dr. Samuel A. Levine Joseph H. Pratt Diagnostic Hospital.  
\*10:00 a.m.-12:00 m. Medical Staff Rounds Peter Bent Brigham Hospital

#### MONDAY, MARCH 22

12:00 m. Clinicopathological Conference Margaret Jewett Hall Mt. Auburn Hospital, Cambridge  
\*12:15-1:15 p.m. Clinicopathological Conference Peter Bent Brigham Hospital

#### TUESDAY, MARCH 23

\*12:15-1:15 p.m. Clinicoroenigenological Conference Peter Bent Brigham Hospital  
\*1:30-2:30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children, Massachusetts General Hospital  
8:00 p.m. Norfolk District Medical Society Boston Medical Library

#### WEDNESDAY, MARCH 24

\*9:00-10:00 a.m. The Etiology of Simple Goiter Dr. Monte A. Greer Joseph H. Pratt Diagnostic Hospital  
\*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital  
\*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services Amphitheater, Children's Hospital

\*Open to the medical profession

MARCH 12 and 13 American Association of Pathologists and Bacteriologists Page 204 issue of February 5

MARCH 16 Greater Boston Medical Society Notice above

MARCH 23 Norfolk District Medical Society Notice above

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons-American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists American Association of Industrial Nurses Inc. and American Association of Industrial Dentists. Hotel Statler, Boston

APRIL 7, 9, 14 and 16 American Trudeau Society Page 240 issue of February 12

APRIL 8 Endometriosis Dr. John Fallon Pentucket Association of Physicians 8:30 p.m. Haverhill

APRIL 10 American Congress of Physical Medicine Page 344 issue of March 4

APRIL 12 Harvard School of Public Health Notice above

APRIL 13 Harvard Medical Society, Amphitheater, Building D Harvard Medical School

APRIL 19-23 American College of Physicians Page xiii, issue of July 31

APRIL 29-MAY 2 American Academy of Pediatrics Page 240 issue of February 12

MAY 6 Suffolk Censors' Meeting Page 344, issue of March 4

MAY 6-8 American Association for the Study of Goiter Page xiii, issue of July 31

MAY 16-22 American Board of Obstetrics and Gynecology Inc. Page 344 issue of March 4

MAY 16-23 International College of Surgeons Page 136, issue of January 22

MAY 17-20 American Urological Association Hotel Statler, Boston

MAY 18-22 American Association on Mental Deficiency Copley Plaza Hotel Boston

MAY 20-25 American Board of Ophthalmology Page 170 issue of January 29

(Notices concluded on page xv)

## NOTICES (Concluded from page 384)

- MAY 25-27 Massachusetts Medical Society Annual Meeting, Hotel Statler Boston
- JUNE 21 and 22 American Society for the Study of Sterility Page 384
- JUNE 28-30 American Academy of Pediatrics, Hotel Schroeder Milwaukee Wisconsin
- JULY 12-17 First International Poliomycelitis Conference Page 36 Issue of January 1
- AUGUST 11-21 International Congress on Mental Health Page 344 Issue of March 4
- SEPTEMBER 13-15 American Academy of Pediatrics, Olympic Hotel Seattle, Washington
- SEPTEMBER 20-23 American Hospital Association Page 310 Issue of February 26
- SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 Issue of January 29
- OCTOBER 6-9 American Board of Ophthalmology Page 170 Issue of January 29
- NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte Haddon Hall Hotel Atlantic City New Jersey

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

MAY 11 Annual Meeting, Hotel Weldon Greenfield

## MIDDLESEX EAST

MARCH 24  
MAY 12 Annual Meeting.  
Meetings will be held at the Bear Hill Golf Club Wakefield

## NORFOLK

MARCH 23 Harvard Night

## PLYMOUTH

MARCH 18, Goddard Hospital Brockton  
APRIL 15 State Farm, Bridgewater  
MAY 20, Lakeville Sanatorium, Lakeville

## SUFFOLK

MAY 6, Censor Meeting

## WORCESTER

APRIL 14 Worcester Hahnemann Hospital  
MAY 12 Annual Meeting

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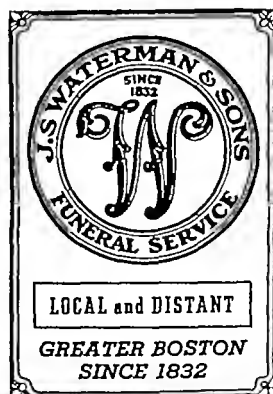
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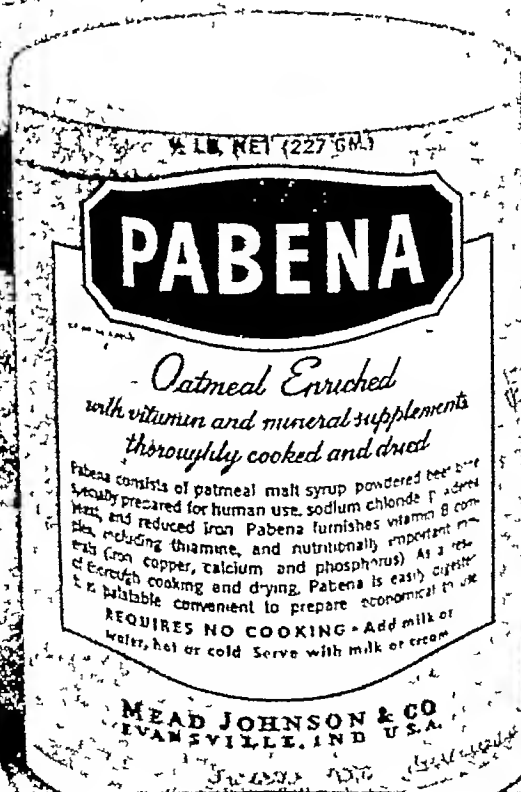
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## LATE REACTIONS TO METALLIC FOREIGN BODIES\*

THOMAS W. BOTSFORD, M.D.,† AND D. RICHARD FREN, M.D.‡

WEST ROXBURY, MASSACHUSETTS

**F**EW military or civilian surgeons have allowed a wound to heal around a metallic foreign body without wondering what the eventual outcome would be. Will the foreign body migrate, act as a focus of infection or cause pain, or will it become encap-

sulated and cause no symptoms? Today, many veterans have foreign bodies imbedded in various regions of the body, and in the months since the cessation of hostilities, we have had the opportunity of studying and treating a few late reactions caused by such bodies. This communication presents observations on a group of 40 patients who have

been treated at the Veterans Administration Hospital in West Roxbury, Massachusetts. The types of reactions encountered and their management are emphasized. It is of principal interest that each patient included in this study had a long and asymptomatic period between the date of recovery from the original wound and the onset of the symptoms for which he was hospitalized. Late reactions to foreign bodies are not a new phenomenon, for observations have been made concerning them after nearly all wars. However, the problem merits renewed in-



FIGURE 1. Lateral Roentgenogram of Pelvis in Case 11 Showing Position of Foreign Body on August 7, 1946

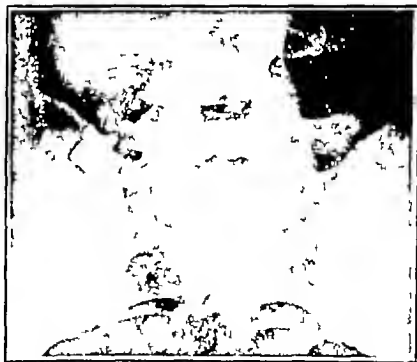


FIGURE 2. Anteroposterior Roentgenogram of Pelvis in Case 11 Showing Position of Foreign Body on August 7, 1946

ulated and cause no symptoms? Today, many veterans have foreign bodies imbedded in various regions of the body, and in the months since the cessation of hostilities, we have had the opportunity of studying and treating a few late reactions caused by such bodies. This communication presents observations on a group of 40 patients who have

terest because of its greater frequency and because of improved technic in the management of metallic foreign bodies and their complications.

When a nonabsorbable foreign body is imbedded in soft tissue it becomes gradually surrounded by a fibrous capsule.<sup>1</sup> If pathogenic micro-organisms are present and are uninhibited, an abscess and a chronically discharging sinus tract may be established, this reaction may be immediate or delayed,

\*From the Surgical Service, Veterans Administration Hospital, West Roxbury, Massachusetts. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

†Instructor in surgery, Harvard Medical School; attending surgeon, Veterans Administration Hospital.

‡Senior resident surgeon, Veterans Administration Hospital.



and its severity will depend on the virulence of the offending organism.<sup>1</sup> Foreign bodies may remain encysted for many years without causing symptoms, as in Paschal's<sup>2</sup> patient, who had an Indian arrow-head embedded in his chest wall for sixty-one years without symptoms. This case is an exception, because as a general rule the patient who knows that he has an imbedded foreign object is more apt to have symptoms than one who is not aware of having a foreign body.<sup>3</sup> Bizarre migrations of foreign bodies occur, and Christopher<sup>4</sup> has noted many unusual

bedded foreign bodies. The information concerning these patients is summarized in Table 1. All the patients in this series were male veterans of World War II who had been wounded by enemy action. They were all in the third decade of life

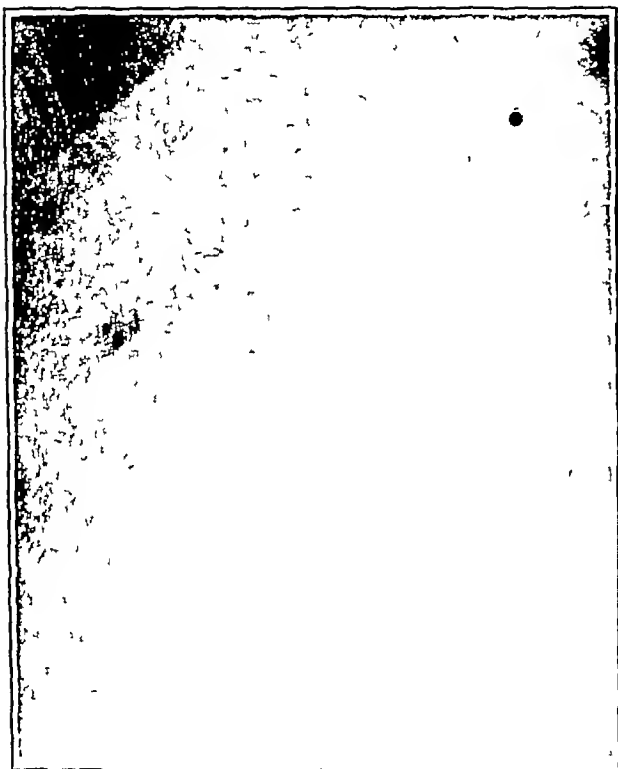


FIGURE 3 *Lateral Roentgenogram of Pelvis in Case 11, Showing the Changed Position of the Foreign Body on April 9, 1947. The foreign body migrated from opposite the superior anterior edge of the fifth lumbar vertebra to below the level of the sacrum in a period of eight months.*

examples. Migration of foreign bodies usually occurs when the body is a sharp, narrow object such as a needle. However, 1 of our patients (Case 11) exhibited migration of a piece of shell fragment that was almost square (Fig 1, 2, 3, 4 and 5). Michael<sup>5</sup> has described a characteristic type of histologic foreign-body reaction to high-explosive shell fragments, but he makes no mention of the clinical application of this finding.

Between June 1 and December 31, 1946, of 1269 patients admitted to this hospital for surgery, 40\* presented symptoms referable to war wounds in which there were retained metallic foreign bodies. Of this group, we have selected 11 patients in whom the symptoms were unequivocally caused by im-

\*Since this paper was submitted for publication 23 additional patients with foreign bodies have been seen. 11 of whom have had their foreign bodies removed. Six patients had infection associated with the foreign body, and 5 had pain.



FIGURE 4 *Anteroposterior Roentgenogram of Pelvis in Case 11, Showing the Foreign Body to Have Migrated Laterally and Completely across the Right Sacroiliac Joint. This film was made on April 9, 1947. The migration occurred over a period of eight months.*

Nine patients had foreign bodies imbedded in other regions of the body than those mentioned in the table. For purposes of simplification and since the foreign bodies were not causing symptoms, they



FIGURE 5 *Photograph of the Foreign Body (Shell Fragment) Removed in Case 11.*

were not included in the table. The patients were all psychologically stable men who had been separated from the service after all their wounds had healed. The foreign bodies in all cases except 1—

a metal ring from an infantry pack — were shell fragments varying from 0.2 to 3 cm in greatest length. The foreign bodies were all located in skeletal muscle, except 1 in the liver. Six were in the lower extremity, 1 in the chest wall, 1 in the buttock, 1 in the iliopsoas muscle, and 1 in the lumbar region.

The interval between the date of healing of the initial wound and the onset of secondary symptoms varied from five to seventeen months. This fact was of especial interest, since 7 patients presented signs and symptoms of infection, and only 4 had pain alone without infection around the foreign body.

### MULTIPLE FOREIGN BODIES, WITH CELLULITIS

There were 3 patients in this group, each with multiple, minute, metallic fragments imbedded in the leg. The following case report is typical.

**CASE 3.** S. M., a 24-year-old former infantry man, was admitted to the hospital complaining of chills, fever, and swelling of the left leg of 24 hours duration. In March 1945, he had been wounded in both legs and in the abdomen by enemy action. The leg wounds had been closed secondarily and were firmly healed 2 months after the date of original trauma. Three months later he had an attack of cellulitis of the left leg which was treated by heat, elevation and parenteral ad-

TABLE 1 Pertinent Data in Patients with Embedded Foreign Bodies

CASE No.	AGE	CAUSATIVE AGENT	TYPE OF FOREIGN BODY	DATE OF INITIAL WOUND	SYMPTOM DATE LEFT LEG	ANATOMICAL LOCATION	SIGNS AND SYMPTOMS	CULTURE OF FOREIGN BODY	TREATMENT	RESULT
1	29	Shell fragments	Multiple	12-2-44	1	Left thigh and 1 in	Fever, pain and cellulitis	None performed	Penicillin and local heat	Improvement
2	24	Shell fragments	Multiple	1-11-45	1	Left thigh	Fever, pain and cellulitis	None performed	Penicillin and local heat	Improvement
3	22	Shell fragments	Multiple	3-27-45	3 at J 16, and 18	Left leg	Fever, pain and cellulitis	None performed	Penicillin and local heat	Improvement
4	26	Land mine fragments	Single	2-27-45	7	Left foot	Pain and callus formation	None performed	Removal	Cure
5	27	Shell fragments	Single	11-10-44	1	Right thigh	Draining sinus	<i>Aerobacter aerogenes</i>	Removal	Cure
6	24	Shell fragments	Single	5-10-45	12	Right shoulder	Local pain	None performed	Removal	Cure
7	28	Machine-gun bullet	Single	8-12-44	12	Right chest wall	Local pain	No organism	Removal	Cure
8	27	Shell fragments	Multiple	4-4-45	9	Liver	Pain, fever and abdominal mass	Hemolytic streptococcus and <i>Staph. albus</i>	Incision and drainage	Improvement
9	24	Shell fragments	Multiple	11-13-43	16	Left leg	Pain	None performed	Removal	Cure
10	21	Shell fragments	Multiple	11-26-44	6	Right buttock	Abscess	<i>Staph. albus</i>	Incision and drainage	Improvement
11	27	Shell fragments	Single	11-13-44	9	Right iliopsoas muscle	Abscess and sinus tract	<i>Staph. albus</i> <i>Pseudomonas morganii</i>	Incision and drainage; removal at second operation	Cure

We were able to check the Army medical records of the patients and found that the original treatment had followed the same pattern in each case. Penicillin as well as tetanus toxoid had been administered to each patient at the time of the original definitive treatment, the penicillin being continued until the wounds showed no evidence of infection. We cannot satisfactorily explain why infection suddenly occurred around a foreign body months after the wounds had healed. The pathogenic organisms at fault may have reached the site either by the blood stream or lymphatic vessels, or may have been continuously present in a dormant state. No other sites of infection elsewhere in the body, such as furuncles, infected teeth and foot infections, were found as exciting causes.

The patients are classified in three clinical groups, which are discussed separately and are as follows: multiple regional foreign bodies, with cellulitis; single or multiple foreign bodies, with abscess formation; and single foreign body, without infection but with pain.

ministration of penicillin. He was asymptomatic until the time of admission 16 months after the original injury.

Physical examination revealed a well developed and well nourished man who appeared acutely ill. The heart and lungs were normal. The abdomen was normal except for two well healed operative scars. The left leg, from the knee to the lower calf, was diffusely reddened and tender, with local edema. There was a long, irregular well healed wound over the lateral aspect of the left leg.

The temperature was 103°F. by mouth, and the pulse 100.

Examination of the blood showed a white-cell count of 8900. A roentgenogram of the left leg revealed numerous small shadows of metallic foreign bodies (Fig. 6). The diagnosis was cellulitis and multiple foreign bodies of the left leg.

The patient was treated by bed rest, elevation of the left leg and hot moist packs to the inflamed area. Penicillin was given intramuscularly in doses of 40,000 Oxford units every 3 hours. Within 48 hours, the temperature and pulse had subsided to normal and there was rapid improvement in the area of cellulitis. The treatment was continued for 7 days and the patient was discharged asymptomatic, on the 9th hospital day. At that time the leg appeared grossly normal except for the scars previously noted. Two months after discharge he was readmitted with a recurrence of the local cellulitis process. He was treated in the same manner, being hospitalized for 8 days. Again the presenting signs and symptoms cleared, and he has been symptom free for 4 months.

None of the foreign bodies were removed because of their minute size and great number, but the patient responded rapidly to local treatment and penicillin as did 2 patients with similar foreign bodies (Cases 1 and 2). These patients represent a problem in that the foreign bodies are too numerous to remove and yet act as foci for occasional explosive infections. Between attacks there has been no



FIGURE 6 Anteroposterior and Lateral Roentgenograms of Left Leg in Case 3, Showing Multiple Foreign Bodies. These were associated with recurrent bouts of cellulitis.

swelling of the leg or evidence of chronic infection as far as the patients could tell. We could find no lesions on the feet that might have been a portal of entry for pathogenic organisms, although that is a likely explanation for this type of clinical course. Undoubtedly, with multiple foreign bodies such as these, considerable scar tissue is present, as well as interference with the local flow of lymph so that any micro-organism entering the leg tends to localize in the damaged region. No bacteriologic studies were made in Case 1 since we did not feel justified in opening an area of cellulitis.

#### SINGLE OR MULTIPLE FOREIGN BODIES, WITH ABSCESS FORMATION

There were 5 patients who had localized infection caused by a foreign body. A typical case is the following:

CASE 8 M M S, a 27-year-old former infantryman, was admitted to the hospital on May 29, 1946, complaining of pain in the right upper quadrant, and of vomiting of 1 week's duration. On April 4, 1945, he had suffered a penetrating wound of the epigastrium and lacerations of the left lobe of the liver, right dome of the diaphragm, transverse mesocolon, stomach and jejunum. The wounds had been sutured, and at operation a shell fragment had been found in the jejunum and removed. The patient had been discharged from the service in August and had been asymptomatic for 9 months. He had spent no time in the tropics or the South.

Physical examination revealed a moderately obese man who appeared acutely ill. A firm, tender mass, measuring 20 by 20 cm, was located about half in the right upper quadrant and half in the epigastrium from the left upper quadrant. The remainder of the physical examination was negative.

The temperature was 101.4° F by mouth, the pulse 88, and the respirations 20.

Examination of the blood disclosed a white-cell count of 15,000, and urinalyses were normal. A plain film of the abdomen showed several small shadows consistent with metallic



FIGURE 7 Anteroposterior Roentgenogram of the Upper Abdomen in Case 4, Showing Two Foreign Bodies in the Region of the Left Lobe of the Liver. (The Other Radio-Opaque Shadows Represent Silver Hemostatic Clips.)

fragments in the region of the left lobe of the liver. The diagnosis was pyogenic liver abscess caused by foreign bodies.

The initial treatment consisted of bed rest, local heat to the abdomen and penicillin (30,000 Oxford units intramuscularly) every 3 hours. Two weeks after entry a large abscess of the left lobe of the liver was drained through an incision in the left upper quadrant. Cultures of the pus revealed hemolytic streptococci and *Staphylococcus albus*. No amebae were present either in the pus or in the stools. After drainage of the abscess, the temperature returned promptly to normal. The penicillin, however, was continued for 3 weeks.

He was discharged improved on July 13 but returned 11 days later with a recurrence of the liver abscess. X-ray films at that time showed that instead of five foreign bodies, there were only two (Fig 7). Drainage was again established, and penicillin again administered. The wound was allowed to close very slowly so that no pocket could develop, and at the end of 11 weeks the patient was discharged. Nine months later he was asymptomatic and without signs of active infection. No foreign bodies were removed at either of these operative procedures. It is probable that several of the small foreign bodies were extruded with the pus that was drained.

In this case the location of the foreign bodies in the liver made their management complicated because of technical difficulties. Even with a Berman locator, these small, deeply situated foreign bodies are difficult to find and remove. In superficial abscesses, such as those in Cases 5 and 9, the foreign

body was removed, since it was not difficult to locate. In Case 10, we were not able to locate the foreign body at the time of drainage of the abscess, and at that time the Berman locator was not available.

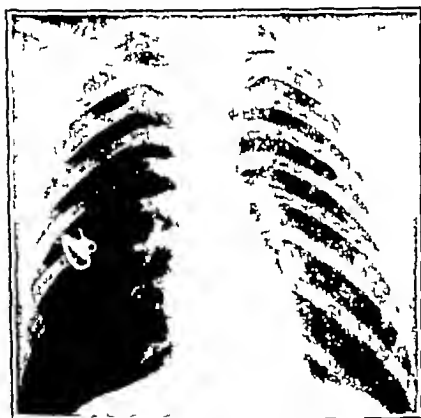
#### SINGLE FOREIGN BODY, WITHOUT INFECTION

The last group consisted of patients who had pain and discomfort referred to the presence of a foreign body, but did not have signs of infection. The following is a typical case.

**CASE 7** I G L., a 28-year-old former medical corpsman, was admitted to the hospital on September 6, 1946, complaining of pain in the right pectoral region of 1 year's duration. On August 12, 1944, he had been wounded to the right pectoral region by an enemy machine-gun bullet. He was hospitalized for 25 days and returned to duty with the wound healed. He was symptom free for 1 year and then began to have pain in the right pectoral region, especially when he used his right arm at work as a machinist.

Physical examination was negative except for a healed wound 3 cm. long and just lateral to the right nipple. There was a diffuse area of thickening beneath the scar measuring 6 by 6 cm. which was tender to palpation.

Anterior and lateral roentgenograms of the chest revealed a ring-shaped foreign body (Fig. 8 and 9) which was removed.



**FIGURE 8** Anteroposterior Roentgenogram of Chest in Case 7 Showing the Shadow of a Metallic Ring Embedded in the Anterior Portion of the Chest Wall

merely knows that a foreign body is present. In Case 7 the location and size of the foreign body undoubtedly accounted for the major part of the symptoms, since the pain occurred in the right pectoral region when the patient raised his right arm or did any strenuous work with the right upper extremity.

#### DISCUSSION

In military surgery, bullets or shell fragments are not usually removed at the time of the initial treatment of the wound or even later unless one or more



**FIGURE 9** Lateral Roentgenogram of the Chest in Case 7 Showing the Shadow of the Metal Ring Embedded in the Right Anterior Portion of the Chest Wall

under ether anesthesia. The object was firmly encapsulated in the pectoralis major muscle and was found to be a ring from an Army pack. Cultures of the area showed no growth. The wound healed by first intention, and the patient was discharged on the 8th postoperative day. He has been asymptomatic since removal of the foreign body.

The treatment of this type of foreign-body reaction may be very simple or may present a most complex problem. It is difficult to determine whether the pain is due to the damage and cicatrix of the original wound alone or to the wound in addition to the retained foreign body, or whether the patient

of the following indications are present that the foreign body is easily found because of its size or location that it is impinging upon a nerve, blood vessel, tendon, joint or bone, that it is a hazard to life or normal function because of its anatomic location, that it is the cause of pain, or that it acts as a focus of infection. The surgery of foreign bodies includes the entire field of general surgery and all the surgical specialties, and with rare exceptions, it is axiomatic that a foreign body is always more difficult to find and remove than is at first apparent.

In this communication we have emphasized the late reactions that may result from foreign bodies in soft tissues, the majority of which become encapsulated with fibrous tissue and cause no symptoms. A variable number of these patients, however, present the problem of infection and pain many

months after the wound has apparently healed. The management of these cases is not at all simple, since the foreign bodies may be small and so numerous, as in the first group discussed above, that removal is not feasible or even wise. If each fragment were removed the trauma of the operation would be extreme. On the other hand, when there is only a single foreign body its removal can be carried out in spite of technical difficulties, and if there are symptoms attributable to this foreign body, removal is necessary in most cases.

A plan for the management and study of these problems includes the basic principles of foreign-body surgery. In the first place the history and physical examination are carefully evaluated to determine the part the foreign body may play in the clinical picture. It must be remembered that the injury of the tissues may be the cause of the symptoms and that the foreign body itself may be only an innocent bystander. A review of the Army medical record is helpful in this respect. Secondly, roentgenologic studies of the location of the fragment are essential before any attempt of removal is made. Thirdly, a decision must be made whether or not to administer penicillin or sulfadiazine. Our policy has been to give penicillin to patients who present signs of infection as soon as they enter the hospital. In cases in which there is no sign of infection and removal is contemplated, penicillin is started on the day prior to operation and continued until the wound is healed. We have given booster doses of tetanus toxoid in all cases. Fourthly when removal of the foreign body is performed, the entire fibrous capsule is removed with the foreign body. Histologic study of the excised material to determine the presence or absence of other foreign matter, such as cloth, should be carried out, in an attempt to prove or disprove the presence of nonopaque material as a factor in the presenting symptoms. Finally, anaerobic and aerobic cultures of the foreign body are made in the operating room. Careful bacteriologic studies in these cases may do much to clarify the late septic reactions. In patients who have multiple small fragments with cellulitis, such as those in the first group discussed above, special attention should be paid to the search for lesions elsewhere, — for example, foot infections, — which may be the portal of entry for intermittent explosive infections.

The basic principles of foreign-body surgery are accurate localization and the control of infection. No attempt at surgical removal should be made until these two factors are properly considered. The use of antibiotics, sulfonamides, tetanus immunization and antitetanic serum have made the surgical technic in these potentially infected, if not actually septic, wounds much safer.

The most accurate localization of the foreign body prior to surgical procedures is paramount. Every surgeon knows that a search for a seemingly easily

accessible foreign body may end in failure. The necessity of accurate localization has led to many an ingenious method of using the roentgenogram and fluoroscope. Films made in two planes with skin markers and two-needle localization under fluoroscopic control are common methods of localization. Reid and Black<sup>6</sup> have described methods of roentgenologic localization. Removal of radio-opaque foreign objects under direct fluoroscopic control is excellent in such regions as the hand and foot, but prolonged exposure of the patient and the operator to the roentgen rays must be carefully guarded against. The Berman "locator" introduced by Moorhead<sup>7</sup> is a surgical divining rod for accurate localization of metallic foreign bodies. It is simple to use, is a sensitive instrument and should be part of the standard armamentarium for surgical removal of metallic foreign bodies. From our experience we are convinced that the "locator" is an important contribution to this particular field of surgery. With the aid of the "locator," the search for the foreign body is greatly shortened in time, and much trauma is avoided. In Case 2 the piece of shell fragment had migrated to the right psoas muscle and was adjacent to the right iliac vessels and the right ureter (Fig 1, 2, 3, 4 and 5). The "locator" pointed exactly to the metallic object, the search for which would have been prolonged, dangerous and even unsuccessful in spite of its fairly large size. An attempt to remove the same foreign body had ended in failure several months before.

### SUMMARY

The problem of late reactions to metallic foreign bodies is presented because of the increase in its incidence after World War II and because of the improvement in its management.

It is probable that there will be an increasing number of such cases in the next few years. Observations on the operative treatment on 11 patients out of a total of 40 are presented, showing that the reactions may be classified into three groups: multiple regional foreign bodies, with cellulitis, single or multiple foreign bodies, with abscess formation, and single foreign body, with local pain. A plan of management is outlined in which the importance of accurate localization and control of infection is stressed.

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## CAPILLARY FRAGILITY AND DIABETIC RETINITIS\*

With a Note on the Use of Rutin

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**A**N INCREASED incidence of retinal changes among patients with diabetes has been noted in recent years. Diabetes of long duration has been associated with the greatest increase in retinal hemorrhages, although hypertension or other evidences of generalized vascular or renal disease may be present or develop subsequently. The importance of this subject is well known to students of diabetes and to internists, who see increasing numbers of diabetic patients, old and young, with impaired vision from this cause.

The term "capillary vessels" includes the endothelial tubing that lies between the arterioles and the small veins. There is no marked distinction between the smallest capillary arteries, the capillary itself and the venules — Lewis calls them collectively "minute vessels."

The explanation of the cause and nature of increased capillary fragility is obscure. A careful discussion of the skin manifestations is given by Peck and Copley.<sup>1</sup> This phenomenon may occur under a variety of circumstances. Poisons, metabolic substances and vitamin deficiencies directly affect the endothelium. Physiologic variations affect the tonus of the capillaries or indirectly damage the endothelium. Capillary permeability is said to be increased in tuberculosis and in some diseases of the skin. In 1944 the capillary fragility in 18 per cent of 265 selected cases of hypertension was found by Griffith and Lindauer<sup>2</sup> to be increased. Persons with abnormal indexes were believed to be predisposed to retinal and cerebral hemorrhages. Patients with high blood pressure, when treated with thiocyanate, developed a further increase in fragility. Beaser<sup>3,4</sup> studied the capillary fragility in diabetic subjects, the test showed a greater incidence of increased capillary fragility in patients in the fifth and sixth decades and in those with hypertension. Paterson<sup>5-7</sup> discussed capillary rupture with intimal hemorrhages in the causation of cerebral vascular lesions and studied also the vascularization and hemorrhages of the intima of arteriosclerotic coronary arteries.<sup>8</sup> Low capillary resistance was found in 30 of 120 diabetic patients in the University Hospital at Ann Arbor, Michigan, and diabetic retinitis proved to be the most frequently associated abnormality in such cases.<sup>9</sup>

In vitamin C deficiency it is supposed that the loss of the intercellular cement permits extravasation. A relation between low ascorbic acid content in the blood plasma and strength of the cutaneous capillaries in healthy children was seen by Ahlborg and Braute.<sup>10</sup> Greene<sup>11</sup> evaluated the capillary-resistance test in the diagnosis of subclinical scurvy and concluded that a positive reaction does not necessarily denote an insufficient vitamin C intake. At the New England Deaconess Hospital Sebesta, Smith, Fernald and Marble<sup>12</sup> determined the vitamin C blood level of 77 adults with diabetes and found both normal blood values above 0.8 mg per 100 cc and an excretion of the urine of more than 400 mg of ascorbic acid in response to a 1000-mg dose given intravenously. To test the possible relation between vitamin C in the blood and capillary fragility in these patients, a series of simultaneous determinations were made, and it was evident that no relation appeared between the vitamin C content of the blood and the capillary fragility.

Scarborough and Stewart<sup>13</sup> claim that the administration of hesperidin can reduce the number of hemorrhages in patients with vitamin P deficiency. The existence of vitamin P was postulated in 1936 by Szent-Györgyi,<sup>14</sup> who claimed that extracts of Hungarian red pepper and lemon juice contained a substance called citrin or vitamin P.

Studying the deficiency of vitamin C and vitamin P in man, Scarborough and Stewart state that administration of vitamin P does not control the large subcutaneous hemorrhages characteristic of the scorbutic state, these hemorrhages were arrested within twenty-four hours by large doses of ascorbic acid. Vitamin P can produce an increased capillary resistance in the scorbutic subject either before or after treatment with vitamin C. The authors believe that a deficiency of this vitamin may exist in man even after large doses of vitamin C.<sup>15</sup> At the moment it must be admitted that evidence for the clinical value of vitamin P in the absence of a deficiency of this vitamin is scanty.

Rutin, another flavone glucoside, is believed to influence capillary fragility. Rutin is a rhamnogalactoside of quercetin, a derivative of flavanol. It is a tasteless, yellow, nontoxic powder, consisting of masses of microscopic needle-like crystals.<sup>16</sup> Both rutin and hesperidin are constituents of plants — garden rue, tobacco and so forth — and are similar in structure. The chemistry of both is

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described by Couch, Naghski and Krewson,<sup>17</sup> of the Eastern Regional Research Laboratory in Philadelphia. Rutin was first isolated from tobacco. The glucoside was prepared from the flure-cured type of high quality. It was expensive, but the cost is now within the reach of most patients. In an attempt to find a still more economical source of the drug, a number of plants were examined for rutin content, and buckwheat was discovered to be the most promising source.<sup>17</sup>

Several reports have indicated that rutin restores abnormal capillary fragility. Griffith, Couch and Lindauer<sup>18</sup> gave rutin in cases of hypertension, without toxic effects that could be attributed to rutin, nor was there any significant change in blood pressure, and capillary fragility became normal in 8 patients within two months of the beginning of medication. The authors also studied the relation between rutin and crude hesperidin in hypertensive subjects with increased capillary fragility.<sup>18</sup>

Shanno<sup>19</sup> considered rutin more efficacious than hesperidin. He recommended its use in cases of hypertension to maintain normal capillary fragility to prevent vascular accidents. A remarkable change in the character of the bleeding of patients with hereditary hemorrhagic telangiectasia was observed by Kushlan<sup>20</sup> after rutin therapy. These reports indicated that rutin is the most active of chemically related compounds that over the past years have been extracted from various plants. One should consider the use of rutin in any condition associated with an increase of capillary fragility.<sup>21, 22</sup>

Since this botanical drug became available for the treatment of abnormal capillary fragility, we have used it in several cases in which there was evidence of diabetic retinitis and high degrees of capillary fragility. Our studies show that capillary resistance is definitely low in practically all persons with diabetic retinitis. We suggest the desirability of further trial of this substance. More important, however, is the possibility that, through further investigation of the pharmacology of rutin, we may ascertain the indications of its early use, in the hope of preventing the capillary damage related to the retinal and perhaps other degenerative complications in subjects with diabetes of long duration.

#### METHODS OF DETERMINATION OF CAPILLARY FRAGILITY

The correct determination of capillary fragility is essential in the selection of patients for rutin therapy. Peck and Copley<sup>1</sup> discussed a considerable variety of methods by which capillary fragility may be tested, including the suction or negative-pressure method, the positive pressure based on the Rumpel-Leede phenomenon, the direct microscopical observation of the vessel at the end of the nail bed, the puncture and bleeding tests, and the skin tests that employ snake venom.

In measuring capillary resistance, we must consider possibly conflicting results due to differences in technics used by various workers. Cutter and Marquardt<sup>23</sup> studied capillary fragility on the end of the nail bed. Moloney,<sup>24</sup> studying capillary fragility in the newborn, used the negative-pressure resistometer. Beaser<sup>3</sup> concluded that negative-pressure methods are unreliable and that positive-pressure tests, such as Göthlin's method, are commendable. Greene<sup>11</sup> chose the Göthlin method when studying subclinical scurvy. Griffith et al.,<sup>2</sup> of the Eastern Regional Research Laboratory, employed the Göthlin technic in their interesting investigation of hypertension. This procedure requires only a blood-pressure cuff, a magnifying glass and a good light. In the present report we followed the Göthlin positive-pressure test, the technic of which is as follows:

A circular area, 6 cm in diameter, is marked in each antecubital space.

A standard blood-pressure cuff is placed on the arm and a pressure equivalent to 35 mm of mercury is maintained for fifteen minutes. The pressure is lowered, and all the petechiae within the circular area are counted, a good magnifying lens being used.

The process is repeated on the other arm, a cuff pressure equivalent to 50 mm of mercury being employed for the same period. The pressure is lowered, and the findings are noted.

To determine the petechial index, the number of petechiae in the first stage is multiplied by 2, and the number accumulated in the second stage is added. The normal index is 8 (or less), an increased value is 13 (or more), and a borderline (probably increased), 9 to 12.

The present communication is concerned with results of the test for determining the capillary fragility in diabetic patients at the New England Deaconess Hospital. The findings reported deal with three groups of patients: nonselected diabetic patients, diabetic subjects selected with varying degrees of retinopathy, and patients with diabetic retinitis or retinitis proliferans and high degrees of capillary fragility who were treated with rutin.

#### MATERIAL AND METHOD

One hundred unselected young and old diabetic patients, male and female, with short and long durations of the disease, with and without complications, who were routinely studied in the hospital wards and in a diabetic nursing home, had a measurement of capillary fragility by the petechial index of Göthlin, described above.

In 56 selected patients with diabetic retinopathy, the capillary fragility was studied by the same petechial index, with certain minor modifications.\*

\*To save time in these 56 patients the blood pressure cuff was placed on both arms at the same time.

Rutin\* was administered to 70 patients with retinitis and increased capillary fragility, only 20 of whom were adequately followed. The initial dose of rutin was 20 mg three times a day, in the 20 patients adequately followed, the dosage was increased to 40 or 60 mg three times a day.

In all the 156 patients the history was taken and physical examination performed by various members of the medical staff. The presence of retinitis was ascertained by careful ophthalmoscopic examination. In the patients under rutin therapy, the examination was followed by the ophthalmologist, and special attention was paid to the retinal damage and the visual field.

#### RESULTS IN 100 UNSELECTED DIABETIC PATIENTS

The capillary fragility was found to be increased in 44 patients (40 per cent), borderline in 4 (4 per cent) and normal in the remaining 56 (56 per cent).

#### Increased Petechial Index

Diabetic retinitis and hypertension were the most closely related abnormalities among the 40 patients with increased capillary fragility (Table 1).

TABLE 1 Abnormalities in Diabetic Patients with Increased Capillary Fragility

ABNORMALITY	NO. OF PATIENTS	PERCENTAGE
Retinitis with normal blood pressure	14	35
Retinitis with hypertension	12	30
Hypertension only	11	27
Normal fundi with normal blood pressure	3	7.5

The relation of increased capillary fragility to retinitis and hypertension is remarkable. In consideration of this fact, we must mention again the similar results reported by Griffith and Lindauer,<sup>2</sup> Beaser,<sup>3</sup> Rudy and Beaser<sup>4</sup> and Wilder.<sup>5</sup> The following is a review of this group of 40 diabetic subjects in whom the capillary fragility was found to be abnormal.

**Retinitis with normal and high blood pressure**  
Twelve patients (30 per cent) with increased petechial counts had retinitis with hypertension and 14 (35 per cent) had retinitis with normal blood pressure. Table 2 lists the 26 diabetic patients with retinitis with and without hypertension. Among these patients, 13 were women, and 13 men. Six male patients had retinitis proliferans, and in only 2 female patients was this severe degree of retinopathy observed. In the whole group of 8 cases with retinitis proliferans the blood pressure was normal in 2 and above 150 systolic, 90 diastolic, in the remaining 6. Five were men under the age of forty with long duration of diabetes. In all 26 patients, 15 were over and 11 under forty years of

age. The duration of diabetes was eighteen and a third years in the younger and only thirteen and a fifth years in the older group.

**Retinitis with hypertension only** Table 3 presents 11 cases in which hypertension was present with an

TABLE 2 Pertinent Data in 26 Diabetic Patients

CASE NO.	AGE	SEX	DURATION OF DIABETES	FUNDUSCOPIC EXAMINATION	BLOOD PRESSURE	CAPILLARY FRAGILITY
2962	36	F	23	Retinitis	Normal	64
2931	29	F	23	Retinitis	Normal	128
26408	49	F	16	Retinitis	Normal	118
12974	62	F	16	Retinitis	Normal	48
24586	23	F	13	Retinitis proliferans	Normal	300
17011	21	F	8	Retinitis	Normal	77
8973	58	F	26	Retinitis	Normal	39
5723	61	F	24	Retinitis	High	101
23711	54	F	7	Retinitis proliferans	H g h	41
2702	65	F	3	Retinitis	High	100
8396	65	F	1	Retinitis	High	48
—	58	F	—	Retinitis	High	44
14943	51	M	27	Retinitis	Normal	400
17943	55	M	23	Retinitis	Normal	95
8403	69	M	8	Retinitis	Normal	21
19102	66	M	9	Retinitis	Normal	210
8771	46	M	10	Retinitis	Normal	47
4763	51	M	23	Retinitis	Normal	90
11077	36	M	22	Retinitis proliferans	High	74
4162	29	M	22	Retinitis proliferans	High	19
2 728	39	M	19	Retinitis proliferans	High	141
2 9030	31	M	9	Retinitis proliferans	High	32
12513	23	M	12	Retinitis	High	66
14044	66	M	10	Retinitis proliferans	Normal	115

increased capillary fragility but in which no retinal damage was observed.

Griffith and Lindauer<sup>2</sup> found low capillary resistance in 18 per cent of 265 cases of hypertension. In our group of nonselected diabetic persons, the in-

TABLE 3 Pertinent Data in 11 Diabetic Patients

CASE NO.	AGE	SEX	DURATION OF DIABETES	CONDITION OF FUNDI	BLOOD PRESSURE	CAPILLARY FRAGILITY
8560	29	F	16	Normal	High	82
28626	70	F	1	Normal	High	14
—	62	F	—	Normal	High	110
—	56	F	—	Normal	High	90
11562	50	F	21	Normal	High	20
—	64	F	—	Normal	High	74
28490	67	M	10	Normal	H g h	23
28501	64	F	32	Normal	High	18
28522	48	F	1	Normal	High	17
29073	59	F	2	Normal	High	16
24710	79	F	3	Normal	High	135

cidence of poor capillary resistance with hypertension was 27.5 per cent. The patients were in most cases women in the fifth, sixth or seventh decade of life and with long duration of diabetes. It should be noted regarding the patients in this group that further examination of the fundi must be done over an extended period to observe any changes, especially in cases like the first patient listed in Table 3, a woman aged twenty-nine with diabetes of long duration who showed normal fundi but had hypertension, edema, moderate albuminuria and capillary fragility of 82 petechiae.

\*Obtained from the Eastern Regional Research Laboratory, Philadelphia.

†By hypertension is meant a blood pressure reading of over 150 systolic and 90 diastolic.



*Increased capillary fragility with normal fundi and normal blood pressure* In 3 cases (75 per cent) abnormal capillary fragility was found in patients with normal blood pressure and normal fundi (Table 4). The first 2 patients were ambulatory women with uncomplicated diabetes admitted for routine check-up. The third, a sixty-seven-year-old woman with diabetes of forty years' duration, was admitted as an emergency in mild acidosis and hematemesis of unknown origin (x-ray studies of the gastrointestinal tract and gastroscopy were negative, and coagulation and prothrombin time were normal, but the gastric acidity, as is often observed in

TABLE 4 *Pertinent Data in 3 Diabetic Patients*

CASE No	AGE	SEX	DURATION OF DIABETES	CONDITION OF FUNDI	BLOOD PRESSURE	CAPILLARY FRAGILITY
	yr		yr			
24872	48	F	29	Normal	Normal	14
27565	47	F	4	Normal	Normal	14
6562	67	F	40	Normal	Normal	48

diabetic patients, was below the normal limits), she had also an ulcer in a neurotrophic right foot and the Göthlin count showed 48 petechiae. Later, other youthful diabetic patients showed increased capillary fragility when no evidence of arteriosclerosis could be demonstrated by x-ray examination of the aortic, pelvic or leg arteries. This group of young adults (twenty-five to thirty years of age) confirm the judgment that increased capillary fragility may be present in young persons with diabetes of long duration as one of the earliest signs

TABLE 5 *Pertinent Data in 4 Diabetic Patients*

CASE No	AGE	SEX	DURATION OF DIABETES	CONDITION OF FUNDI	BLOOD PRESSURE	CAPILLARY FRAGILITY
	yr		yr			
23234	74	M	25	Normal	High	12
—	41	F	5	Normal	Normal	12
28435	64	F	1	Normal	Normal	10
8246	69	F	17	Retinitis	High	11

of arteriosclerosis, which will subsequently be manifest in nephritis, hypertension and so forth, and general arteriosclerosis.

#### *Borderline Petechial Index*

Griffith and Lindauer<sup>2</sup> found the petechial index to be borderline in 3 cases among a group of 265 cases of hypertension studied. They judge from the occurrence of complications that the borderline group should be called abnormal. In this series of unselected diabetic persons, the capillary fragility was classified as borderline in only 4 cases. Table 5 lists these 4 cases. Two had normal fundi with blood pressures above normal, the duration of

diabetes was five years in one and twenty-five years in the other. A woman aged sixty-nine with diabetes of seventeen years' duration and with hypertension and retinitis is in this group of borderline cases. The use of rutin is suggested in diabetic patients whose petechial counts appear to be borderline.

#### *Normal Petechial Index*

Among the 56 diabetic patients of this nonselected group who had normal counts, in 54 the fundi were normal and only in 2 cases was retinal damage present. A twenty-two-year-old girl with diabetes of fourteen years' duration (Case 28922) and with retinitis proliferans, hypertension, nephritis, gangrene in the right foot, anasarca and uremia had a petechial index of 7. A seventy-three-year-old woman with retinitis proliferans and normal blood pressure (Case 46334) had only 3 petechiae. In a summary of this group of 100 diabetic patients measured by the Göthlin technic, it was found that the index of capillary fragility was above normal in practically all patients who had diabetic retinitis. It seems clear from our observation that diabetic retinopathy seldom occurs in patients who do not have some degree of increased fragility of the capillary walls.

#### RESULTS IN 56 ADDITIONAL DIABETIC PATIENTS WITH RETINOPATHY

That there is a loss of the resistance of the capillary wall in diabetic persons is definite, and it is more evident when one studies selected diabetic patients with early or advanced retinopathy. The distinction between the two is of degree and stage of development. The proliferative type of retinitis often follows a period in which the typical central punctate hemorrhages of diabetic retinitis have been present for months or years. This picture constitutes the most serious menace, aside from arteriosclerosis, nephritis and hypertension, that persons with diabetes of long duration have faced.

In the hope of obtaining the new light on this subject that is so greatly needed, we studied an additional group of 56 selected patients with diabetic retinopathy. They were admitted to the hospital for routine check-up, regulation of diet and insulin or treatment of complications. The petechial index was increased in 47 (83.9 per cent) and borderline in 9 (16.1 per cent) and in no case was found to be normal. To this group of selected cases we add the 26 cases from the nonselected group listed in Table 1, making a total of 82 diabetic patients with retinopathy. The weakening of the capillary wall among these patients is definite, as shown by borderline petechial index in 9 cases and increased petechial index in 73.

#### *Sex*

Studying the effect of diabetes in the development of degenerative vascular diseases, Dry and Hines,<sup>6</sup> found enormously increased vulnerability among

women Schneider et al.<sup>27</sup> who studied the plasma proteins in diabetic retinitis, state that retinitis is more frequent in women. In their 31 cases, 26 patients (84 per cent) were women. Griffith and Lindauer, at the Scientific Exhibit of the American Medical Association in San Francisco in 1946, showed that there was no significant relation between capillary fragility and sex in their hypertensive patients. In our 82 diabetic patients with retinitis and increased capillary fragility, no significant predominancy was found among 44 women as compared with 38 men.

### *Blood Pressure*

In these 82 diabetic patients with retinitis, 39 had normal blood pressures and 43 had pressures above 150 systolic, 90 diastolic.

### *Age of Patient and Duration of Diabetes*

The age is an important factor in the consideration of capillary fragility. Moloney<sup>44</sup> found more or less abnormal capillary fragility in 33 of 55 normal infants but this decreased resistance disappeared as the infant became older. Cutter,<sup>22</sup> in normal adults, showed that the fragility of the capillaries increased in direct proportion to age, and Paterson<sup>4-7</sup> states that the influence of age on the elasticity of capillaries may be an important factor in the causation of intimal hemorrhages. We must say, however, that the duration of diabetes appears to be more important. Rudy, Beaser and Seligman<sup>4</sup> reported that the incidence of increased fragility of the capillaries is great in the fifth and sixth decades and that in diabetic patients a greater incidence is observed at each age decade. It is interesting to observe that of the 82 diabetic subjects considered above 34 (41.4 per cent) were under forty years of age and that some were as young as twenty-one years, the duration of the diabetes, however, was generally more than ten years.

Of the entire group of 82 patients 48 were over forty years, with an average duration of eleven and a third years, and in the 34 patients younger than forty years of age, the average duration of diabetes was seventeen and three fourths years.

An abnormal condition of the capillaries may be an important factor in the production of certain vascular complications that occur in persons with diabetes of long duration. We consider it necessary to measure the capillary resistance in persons who have had diabetes for a long time. The importance of its early recognition is evident. This capillary condition will be the advent of the inevitable "period of exhaustion"<sup>28</sup> of the aging diabetic patient, who now lives longer not only with diabetes but also with degenerative diseases.

### RESULTS OF RUTIN THERAPY

Rutin was administered to 70 patients, but only 20 have been followed adequately. The initial dose

was 20 mg three times a day, and in the 20 patients followed, the dosage was increased to 120 or 180 mg daily after one or two months. No selection was made in this group of patients, whose ages were between twenty-three and sixty-one years, with a duration of diabetes from three to forty years. Twelve had blood pressures above 150 systolic, 90 diastolic. Eight had advanced retinitis proliferans, 6 had severe, and 6 had moderate diabetic retinopathy. To determine the effects of the therapy, capillary fragility was measured every month, and special attention was paid to the retinal picture, visual fields, blood pressure and evidences of sensitivity or toxicity from rutin.

### *Capillary Fragility*

The petechial index became normal or borderline in 5 cases (25 per cent), remained positive but improved in 5 (25 per cent) and was not improved in 10 (50 per cent).

The following cases illustrate the effect of rutin therapy in diabetic patients with retinitis.

CASE 24586. A 23 year-old woman with diabetes of 13 years' duration was examined in 1944 by Dr. W. P. Beetham who found extensive retinitis proliferans with marked new capillary formation and sclerosis of the retinal veins, large hemorrhages and a few areas of cotton and waxy exudate. The visual fields were 20/200 on the right and 20/50 on the left. In April 1946, the visual fields were 6/20 on the right and 6/15 on the left, and extensive retinitis proliferans involved a great portion of each fundus. The blood pressure was 118/86, and the capillary fragility index showed at least 300 petechiae. The patient started taking rutin in April and the capillary fragility was regularly determined each month until April 1947. The first reduction occurred 5 months after the beginning of medication, when the index fell to 182 petechiae. The reading was 56 in January 1947 and was within the normal limits in April. Since July 1946 she was definitely under the impression that her vision had improved but as a matter of fact exactly the same visual acuity was obtained and no modification was seen in the retina. The blood pressure continued unaffected and she had no rash or toxic reactions.

CASE 21518. A 43 year-old man with diabetes of 4 years' duration developed typical central punctate hemorrhages with waxy exudate in each fundus. The visual acuity was 6/7 in each eye the blood pressure was 165/90 and the capillary fragility index was 42 in June 1946. The patient received 60 mg of rutin, and the dosage was increased to 120 mg after 3 months. The capillary resistance became normal after 8 months. The retinal damage and visual field remained the same the blood pressure was also unaffected.

In these cases the capillary fragility became normal with rutin treatment. In the first case, a young diabetic patient with long duration of the disease and with general vascular sclerosis, severe retinitis proliferans and a tremendous increase in fragility of the capillaries, after one year under rutin therapy the petechial index became normal. In the second patient, a man with diabetes of four years' duration, early diabetic retinitis and relatively moderate increase in capillary fragility, the petechial index was reduced progressively and reached the normal counting after eight months.

In the results reported by Griffith and Lindauer<sup>28</sup> in hypertensive subjects, the Göthlin test

normal after four months of therapy, whereas in our diabetic patients with retinitis, only 25 per cent showed normal capillary resistance after eight months or more of therapy

### Retinitis

In no case was an improvement of the visual field or in the retinal picture seen, despite the fact that several patients were strongly convinced that rutin had improved their vision. The retinal picture was unchanged in 13 cases. Two patients had subsequent hemorrhages, and 2 had arterial thrombosis while taking rutin, whereas the hemorrhage was absorbed in 3.

In the patients who had new hemorrhages, the Gothlin test remained increased, and in some cases a rise in the index was seen with the new hemorrhages. A good example is provided by the following case:

**CASE 17242** A 56-year-old man with diabetes of 23 years' duration had hypertension and bilateral diabetic retinopathy, typical punctate hemorrhages were present with vitreous opacities in each eye. The visual acuity was 20/70 on the right and 20/200 on the left, and the capillary fragility index in June, 1946, showed 95 petechiae. For 5 months he was taking rutin daily with progressive reduction of the petechial index, and after 8 months of medication new small hemorrhages developed in the left eye, with a new rise in the capillary fragility. The rutin dosage was increased to 120 and 180 mg, followed by marked reduction in capillary fragility, the petechial index actually dropping to normal. This patient was also under the impression that his vision had improved. However, the visual acuity remained exactly the same.

Another example is provided by Case 27954, in a forty-five-year-old man with diabetes of fifteen years' duration and with diabetic retinopathy and extensive vitreous hemorrhages without ocular hypertonus, who had visual acuity of 20/20 in the right eye and in the left merely perceived a flash-light. The capillary fragility was 24 in October, 1946, and remained abnormally high, with the appearance of subsequent new hemorrhages.

### Miscellaneous

Following these 20 diabetic patients under rutin over a period varying from three months to a year, we have observed that the blood pressure in the entire group was unaffected, and no evidences of toxicity or sensitivity to rutin were seen.

Capillary resistance is definitely low in practically all persons with diabetic retinitis. This abnormality tends to decrease while rutin is being taken and the course of the retinitis is not altered as it was hoped. We should say, however, that rutin was given in the main to patients who already had advanced disease. Thus, the importance of the early recognition of this inevitable advent of capillary damage among patients with diabetes of long duration is evident.

We suggest the possibility that this lack of resistance of capillary wall related to retinitis and hypertension is also related to the degenerative complica-

tions — arteriosclerosis and the nephrotic syndrome — that constitute a specter in the prolonged life of the young diabetic patient.

### SUMMARY

The literature on capillary fragility in relation to diabetic retinitis is reviewed.

Measurements of capillary fragility by the petechial index of Göthlin were done in a total of 156 diabetic patients. Forty per cent of 100 unselected diabetic patients showed an increased capillary fragility. This abnormality was found in practically all patients with diabetic retinitis, whether or not hypertension was present. In 11 cases hypertension was present with increased capillary fragility, but no retinal damage was observed.

In 56 selected cases with retinitis no patients showed a normal petechial index. The petechial index was increased in 47 (83.9 per cent) and borderline in 9 (16.1 per cent).

The incidence of increased capillary fragility was related to the duration of the diabetes more clearly than to the age of the patient, 41.4 per cent of 82 patients with retinitis were under forty years of age, and increased capillary fragility was observed as early as the age of twenty-one years, but with long duration of diabetes.

Rutin was administered to 70 patients with retinitis and increased capillary fragility. The initial dose was 20 mg three times a day, and this was increased to 40 or 60 mg three times a day in 20 cases. (A dosage of 300 to 400 mg daily may be used.)

Increased capillary fragility can be brought to normal with the use of rutin in sufficient dosage, although no patient with retinitis was improved. Increased capillary fragility occurs in diabetic patients as an early evidence of generalized arterial disease and is closely correlated with the development of retinitis and later nephritis.

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## FATAL INTESTINAL OBSTRUCTION FOLLOWING INJECTION TREATMENT OF AN INGUINAL HERNIA

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THE injection treatment of hernia is now so little practiced in regular surgical circles in New England that its results, favorable or unfavorable, are rarely observed. This report deals with a patient in whom a complete obstruction of the small intestine was attributable to the inflammatory reaction and adhesions produced by the injection treatment of an inguinal hernia.

### CASE REPORT

H. J., a 57-year-old man, was admitted to the Burbank Hospital, Fitchburg, Massachusetts on June 5, 1946, complaining of abdominal distention and constipation of 2 days duration. This patient had had a reducible right inguinal hernia for several years and was currently receiving a series of injection treatments in a nearby town. He wore a truss in the usual way during the course of treatment. The last injection had been given on the morning of June 3. In the afternoon the patient began to feel ill but had no pain. The abdomen gradually became distended; he lost his appetite, passed no gas and became constipated. That night his wife gave him a dose of castor oil, with no fecal results, and the distention increased. He had no nausea or vomiting but when first seen by his physician 2 days after the onset was complaining of moderately intense cramplike pains in the epigastrium.

Physical examination showed the patient to be dehydrated and somewhat toxic. The cardiovascular system seemed normal, and the lungs were clear. The abdomen was greatly distended and tympanitic throughout. No masses could be felt, and there was no localized tenderness. The right inguinal hernia was of medium size and entirely reducible.

The temperature was 98°F, and the pulse 88. The blood pressure was 150/100.

The urine was concentrated with a specific gravity of 1.026 and gave a + test for albumin but was otherwise normal. Examination of the blood disclosed a red-cell count of 4,910,000, with a hemoglobin of 98 per cent (Sahli) and a white-cell count of 5000 with 65 per cent neutrophils and 35 per cent lymphocytes. The blood osmotic pressure was 32 mg per 100 cc. An x-ray film of the abdomen showed several greatly dilated loops with the typical step-ladder pattern of obstruction of the small intestine.

Attempts were made to pass a Miller-Abbott tube but after 24 hours the tube had not passed through the pylorus even

under fluoroscopic manipulation. During the first 2 days in the hospital the temperature remained nearly normal, the pulse ranged between 80 and 90 and repeated white-cell counts were not greatly elevated. The distention continued, however, and emesis in the hospital produced only a very small amount of fecal and gas return. At the end of 2 days he began to have fecal vomiting and fecal drainage from the Miller-Abbott tube which was then lying in the stomach.

Two days after admission when the patient was first seen by the author the findings were essentially as noted above. The patient was only slightly dehydrated, he appeared somewhat toxic. The abdomen was diffusely and markedly distended and tympanitic. Individual loops of bowel could not be outlined perhaps because of the rather obese abdominal wall. The only area of audible peristalsis was adjacent to the right flank. There was no abdominal spasm and no very definite tenderness. The right inguinal hernia was entirely reducible and also omentum. The hernia protruded again spontaneously when the finger was withdrawn from the external ring with the patient recumbent and with just cough or straining. A provisional diagnosis of obstruction of the small intestine possibly due to the adhesions caused by the injection treatments of the hernia was made.

An exploratory laparotomy was performed through a right paramedian incision. Clear straw-colored fluid poured from the peritoneal cavity and loops of greatly dilated and congested small bowel measuring as much as 8 1/2 cm. in diameter in some places presented in the wound. This dilatation of the intestine extended proximally to the ligament of Treitz and distally to a point in the lower ileum about 30 cm. above the ileocecal valve. At this point the small bowel was adherent to the parietal peritoneum of the right internal inguinal ring margin by several broad adhesions which also tended to force a knuckle of bowel distal to this point into the inguinal canal. These adhesions were fresh and freed without difficulty. Some fibrous exudate was also observed on the bowel in this area. These findings suggested that the whole process was of not more than a few weeks' duration. The bowel appeared perfectly viable. The abdomen was then closed without further procedure and without drainage. No attempt was made to repair the hernia itself, since it was believed that it would be unwise to prolong the operation further. The patient was in good condition at that time however with a systolic blood pressure of 120 and a pulse of 80. There was some excess of tracheobronchial secretions, but this cleared in the Trendelenburg position and the breathings then seemed satisfactory. The patient returned to the ward in good condition but expired suddenly and with almost no warning while still under anesthesia almost 2 hours later. Permission for autopsy could not be obtained.

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## DISCUSSION

As pointed out by Maier<sup>1</sup> in a recent report the treatment of hernia by the injection of sclerosing or irritating solutions evoked a great deal of enthusiasm in this country between ten and fifteen years ago. Its protagonists claimed excellent results with a minimum of complications resulting from the treatment itself. Watson,<sup>2</sup> for example, in the second edition of his textbook on hernia published in 1938, stated that he had performed over five thousand injections on 300 patients with hernia, with 95 per cent cures for small indirect inguinal hernias and between 80 and 90 per cent cures for larger or complicated hernias, similar remarkably good results were noted in several series totaling thousands of cases collected by him from the literature. One is impressed, however, by a lack of follow-up statistics based on acceptable time intervals such as one, two and three years in these reports. Watson claimed no serious complications from injection treatment in his own hands and no case of intestinal obstruction at the time of his report.

In 1937 Burdick and Coley<sup>3</sup> reported from the Hospital for Ruptured and Crippled in New York City their findings in a carefully controlled series of 92 cases of hernias treated by injections in an effort to evaluate accurately the place of this treatment. Although a high percentage enjoyed temporary relief of the hernias, these patients continued to wear trusses, and not 1 case was actually cured at the end of a year. Maier<sup>1</sup> reports from the same hospital on a series of 18 operations performed after previous injection treatments. He found marked scarring and atrophy of muscles and obliteration

of normal tissue planes as a result of the sclerosing injections, which made the dissection and satisfactory repair very difficult. In 1 of these cases, obstruction of the small intestine due to incarceration of the bowel in the inguinal canal was encountered. Maier mentions several other cases of strangulated hernia caused by the unyielding "cartilaginous" internal rings produced by the injections. Rice,<sup>4</sup> an enthusiast ten years ago, now finds only a "narrow field of usefulness (for injection treatment) in slender individuals." It also seems significant that no articles favoring injection treatment have been published from responsible surgical clinics in over five years.

## SUMMARY

A case in which recent intraperitoneal adhesions resulting from the injection treatment of an inguinal hernia caused complete simple obstruction of the small intestine is presented in detail. This appears to be a rare complication of the injection treatment of hernia but should be added to a significant list of complications and sequelae that have been reported in the past.

Fortunately, interest in the injection treatment seems to be waning with the realization that this method cannot be depended on for cure of hernia in general.

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## THE INCIDENCE OF MULTIPLE LESIONS IN PRIMARY SYPHILIS

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ONE of the most popular misconceptions of the medical profession is that the primary lesion of syphilis is always single. In fact, many physicians have been known to eliminate syphilis as a part of the differential diagnosis because the genital lesions were multiple, not single. In our medical-school experience and that of our immediate acquaintances of the medical profession the impression was given that multiple primary lesions in syphilis are rare (in the dozen or so medical schools attended). Medical students and general practitioners can hardly be blamed, since authoritative authors such as Stokes et al.,<sup>1</sup> Sutton and Sutton<sup>2</sup> and Kampmeier<sup>3</sup> declare that multiple chancres are infrequently seen. Andrews<sup>4</sup> and Ormsby and Montgomery<sup>5</sup> mention that chancres are usually single but are frequently multiple.

The limited experience of general practitioners makes them utterly dependent upon these usual sources of knowledge concerning syphilis. Three out of five standard reference books give the impression that multiple chancres border on rarity.

One of us (I.W.K.), while reviewing his medical-school syphilology notes, experienced this impression. As a result, it was decided to determine what the actual figures were at the Kanawha Valley Medical Center, since it was the opinion that multiple primary lesions were not infrequent.

At this clinic we find that multiple lesions are not rare—in fact they are almost as common as single lesions, being approximately 40 per cent of the entire group of cases diagnosed as primary syphilis in 1946. In the literature only two other series of cases were found: Klauder's<sup>6</sup> in 1918 (24 per cent multiple lesions in 200 cases) and Driver's<sup>7</sup> in 1922 (38 per cent in 203 cases). The latter series agrees very closely with our own experience.

In an effort to determine whether these multiple lesions were definitely due to secondary syphilis, we listed separately all untreated, seronegative, dark-field positive cases. This was done in accordance with the general assumption that more than 98 per cent of all cases of secondary syphilis have positive serologic tests. Thus, we have an unselected series of cases that were clinically primary syphilis and a selected series of cases that were still in the seronegative phase. To our amazement an even greater percentage of patients in the latter group had multiple lesions.

In the selection of these cases, penicillin in a small number of doses was not considered as treatment,

whereas arsenicals or bismuth, or both, was considered treatment. The Kahn quantitative serologic test for syphilis, as done by the West Virginia State Hygienic Laboratory, was selected as the index of seronegativity or seropositivity, thereby using a common standard and eliminating various sensitivities—Kanawha Valley Medical Center Laboratory employs the Kahn standard test and Mazzini procedure, in the West Virginia State Laboratory, Hinton, Kolmer and Kahn quantitative tests are done routinely on all admissions.

There was no known bias of the examiners toward single or multiple lesions. At the time the compilation of figures was begun (March, 1947) four of the seven examiners had left this facility, and no such compilation had been anticipated before their departures. Most of the diagnoses were made by five of the seven examiners, and over half by two of them. The period covered was January 1 to December 31, 1946, inclusive.

At Kanawha Valley Medical Center 2023 patients with primary and secondary syphilis, 742 with early latent syphilis and 718 in other stages were admitted. In the unselected cases of primary syphilis the chancres were single in 378 (58 per cent), multiple in 251 (38.5 per cent) and indeterminate<sup>8</sup> in 23 (3.5 per cent). In the selected seronegative cases of primary syphilis the lesions were single in 107 (56.3 per cent), multiple in 82 (43.2 per cent) and indeterminate in 1 (0.5 per cent).

In the untreated seronegative primary cases, there were reinfections in 3, a monorecurrence relapse in 1 and an extragenital lesion (breast of female patient) in 1. In the entire series of primary cases there were reinfections (Stokes criteria were not used by the examiners) in 24, monorecurrence relapses in 16 and extragenital lesions in 10. Of the extragenital lesions observed in this series, only in 1 case were they multiple—so-called "kissing lesions" of the lips. Many extragenital primary lesions were observed, but the majority of patients were admitted in the secondary stage, presumably because of the unfamiliarity of the general practitioners with extragenital lesions and no suspicion of syphilis until a generalized rash appeared.

The oldest patient with primary syphilis was a 75-year-old man, and the youngest a boy of nine. Table 1 compares the sex incidence in selected and unselected cases. As noted many times before, the diagnosis of primary syphilis is made more frequently in male than in female patients. At this center 51.8 per cent of all persons seen (slightly more

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<sup>8</sup>"Indeterminate" signifies that the examiner was unable to determine the number of lesions (usually because of phimosis) or neglected to note the number.

than half) were male patients, but in the unselected series of primary cases 87.3 per cent were male and 12.7 per cent were female patients — almost seven times as many males as females — and in

TABLE 1 *Sex Incidence in Selected and Unselected Cases of Primary Syphilis*

SOURCE OF DATA	MALE PATIENTS		FEMALE PATIENTS	
	NO	PER-CENTAGE	NO	PER-CENTAGE
All patients	51	87.3	48	12.7
Unselected series	87	3	12	7
Selected cases	93	2	6	8

the selected series the male preponderance was even greater 93.2 per cent males to 6.8 per cent females, or almost fourteen times as many (Tables 2 and 3)

TABLE 2 *Sex Incidence in Cases Diagnosed as Primary Syphilis*

SOURCE OF DATA	MALE PATIENTS		FEMALE PATIENTS	
	NO	PER-CENTAGE	NO	PER-CENTAGE
Entire series	569	87.3	83	12.7
Patients with multiple lesions	219	87.3	32	12.7
Patients with single lesions	327	86.5	51	13.5
Patients with indeterminate lesions	23	100.0	0	0.0

Thus, in our series it seems not only that more males seek treatment in the primary stage but also that in the earliest stage of diagnosis of syphilis (the

TABLE 3 *Sex Incidence in Selected Cases Diagnosed as Primary Syphilis*

SOURCE OF DATA	MALE PATIENTS		FEMALE PATIENTS	
	NO	PER-CENTAGE	NO	PER-CENTAGE
Entire series	177	93.2	13	6.8
Patients with multiple lesions	77	93.9	5	6.1
Patients with single lesions	99	92.5	8	7.5
Patients with indeterminate lesions	1	100.0	0	0.0

seronegative, dark-field-positive, primary stage) the preponderance in the male is even greater

It is interesting that despite the wide variance of numbers of males and females, the percentage of

multiple lesions is consistent in both series. In the unselected series 12.7 per cent were females, and 12.7 per cent of those with multiple lesions and 13.5 per cent of those with single lesions were females. In the selected series 6.8 per cent were females, and 6.1 per cent of those with multiple lesions and 7.5 per cent with single lesions were females. Thus, the percentages were of the same orders in both series, and there seems to be no tendency for females or males to have single or multiple lesions more frequently than those of the other sex.

## CONCLUSIONS

Multiple lesions are common in primary syphilis — 38.5 per cent of 652 primary diagnoses being multiple.

In 190 seronegative dark-field-positive untreated cases of primary syphilis 43.2 per cent of patients had multiple lesions.

Persons with multiple primary lesions tend to come for treatment earlier than those with single lesions.

Patients with extragenital primary lesions are seldom treated in the seronegative state.

Primary syphilis is no respecter of age.

The diagnosis in the primary stage of syphilis is made much more frequently in male than in female patients — 87.3 per cent and 12.7 per cent respectively.

Male patients seek treatment earlier than females in primary syphilis (93.2 per cent of the former and 6.8 per cent of the latter in the selected "early" series).

There is no recognized tendency for one sex to have multiple primary lesions more frequently than the other.

Extragenital primary lesions are more frequently single than genital primary lesions.

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## MEDICAL PROGRESS

## DIABETES

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THE following subjects are considered in this progress report on diabetes statistics, diabetic acidosis and coma, the hyperglycemic action of highly purified alkaline phosphatase convulsive states in diabetes, electrocardiographic changes, arteriosclerosis, pregnancy in diabetes metabolism of carbohydrate and fat, the diabetes section of the United States Public Health Service, new rapid blood sugar tests and alloxan diabetes

## STATISTICS

Variations in diabetes mortality in different countries and even in the different states of the United States are so glaring as to arrest attention and demand explanation. Such a diversity of statistical data can be explained partly by different methods of recording deaths, accessibility to medical supervision and availability for statistical enumeration. In this neighborhood the fallacy of estimating the true mortality and much more the computation of the true incidence of diabetes from reports of fatal cases has again been shown by a comparison of the death certificates to a series of deaths of 1000 known diabetic patients only 63.2 were reported as diabetic according to the joint causes of death.<sup>1</sup> The remainder escaped enumeration because of the absence of the word "diabetes" on the certificate, its mention as a secondary cause of death or another disease given priority. Therefore, the Oxford, Massachusetts, survey in which urine and blood specimens of the inhabitants were examined, conducted by Wilkerson and Krall,<sup>2</sup> of the United States Public Health Service, is a major contribution to knowledge of the incidence of diabetes.

The town of Oxford, Massachusetts, has 4983 inhabitants and is diabetes conscious because a children's diabetes camp has been in operation there for seventeen years and these hundred children are an every-day sight on the streets, in bathing or at church. The inhabitants of the town, therefore, were co-operative in the survey, and 3516, or 70.6 per cent, submitted to tests of the blood and urine

For the 40 known diabetic patients in the community prior to the survey 30 persons with unrecognized diabetes were discovered, and if all residents had been examined, the implication is that for each known there was an unknown case of diabetes. Oxford is a representative community, the age composition of the population closely paralleling that of the country as a whole. The incidence of diabetes in the Oxford Survey based on the total population was 0.8 per cent for known cases and 0.6 per cent for newly discovered cases, or a total incidence of 1.4 per cent for the 4983 inhabitants. The ages of the newly discovered diabetic persons

TABLE 1 Prevalence of Diabetes in Oxford, Massachusetts

AGE INTERVAL	TOTAL NO OF PERSONS TESTED	TOTAL NO OF DIABETIC PERSONS
Under 15	931	0
15 to 24	521	2
25 to 34	606	2
35 to 44	444	9
45 to 54	411	19
55 to 64	295	15
65 to 74	192	14
75 and over	69	9
UNKNOWN	2	—

varied between sixteen and ninety-three years, with a median age of fifty-five years, those from forty-five to sixty-four years of age constituting nearly half the cases and more than half the new cases. In the cases in the age decades tested, from forty-five years on, the percentages of diabetic patients found were surprisingly high (Table 1). Thus, between forty-five and fifty-four it was 4.6 per cent, between fifty-five and sixty-four it was 5.1 per cent, and between sixty-five and seventy-four it was 7.3 per cent, rising above the age of seventy-five to 13.0 per cent. If these figures were substantiated by similar figures in larger groups, diabetes would be even a greater geriatric problem than already anticipated.

The sex distribution among the 70 cases revealed 31 men and 39 women. There was a high prevalence of the disease among the French or those of French-Canadian descent. A family history of diabetes was reported by 38.6 per cent of the diabetic and by 18.2 of the nondiabetic persons. Overweight was the rule. The survey showed the unreliability of the fasting blood sugar level as a means of diagnosing early

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diabetes and emphasized the necessity of using both blood and urine tests for diagnosis. If urinalysis alone had been employed 8 cases would have escaped diagnosis, and if only a blood specimen had been taken 6 cases would have escaped detection.

For the group tested in Oxford the screening level for hyperglycemia was 160 mg per 100 cc for venous blood and 190 mg per 100 cc for capillary blood

were not in accord or borderline or if there was persistent hyperglycemia without glycosuria or vice versa. The details are given in the original article, which is replete with valuable data, such as those concerning the known diabetic persons tested between the ages of fifteen and twenty-four. This is the only group in which a large enough number of both venous and capillary specimens

TABLE 2 *Death Rates from Diabetes Mellitus, 1940 (Adapted from Marks<sup>5</sup>)*

GEOGRAPHIC DIVISION	TOTAL DEATH RATE		DEATH RATE FOR WHITES		DEATH RATE FOR NONWHITES	
	ADJUSTED* per 100,000	CRUDE per 100,000	ADJUSTED* per 100,000	CRUDE per 100,000	ADJUSTED* per 100,000	CRUDE per 100,000
United States	26.6	26.6	26.7	27.6	23.2	17.9
New England						
Maine	25.3	32.1	25.3	32.1	†	†
New Hampshire	28.1	37.0	28.1	37.1	0	0
Vermont	27.0	33.7	27.0	33.7	0	0
Massachusetts	29.8	35.7	29.8	35.8	30.1	30.4
Rhode Island	35.4	38.8	35.0	38.5	†	†
Connecticut	32.8	35.8	32.6	35.9	40.8	32.5
Middle Atlantic						
New York	39.0	40.6	38.8	41.2	39.7	27.9
New Jersey	35.6	36.4	34.9	36.2	51.0	39.7
Pennsylvania	35.9	36.3	35.4	36.3	46.5	36.3
East North Central						
Ohio	28.1	31.3	27.6	31.2	39.8	33.4
Indiana	24.2	28.1	23.8	27.9	35.7	33.5
Illinois	32.0	34.1	31.5	34.1	38.9	34.3
Michigan	27.9	26.7	27.7	26.8	32.0	22.6
Wisconsin	26.0	28.4	25.9	28.4	†	†
West North Central						
Minnesota	24.5	26.8	24.4	26.8	†	†
Iowa	23.1	28.4	22.9	28.3	†	†
Missouri	21.6	25.3	21.4	25.5	23.2	22.8
North Dakota	28.7	26.6	28.6	26.6	†	†
South Dakota	23.0	23.2	22.8	23.3	†	†
Nebraska	24.7	28.1	24.8	28.2	†	†
Kansas	21.7	26.0	21.5	25.9	27.3	30.1
South Atlantic						
Delaware	27.6	30.0	26.2	29.5	37.1	33.4
Maryland	31.5	31.2	32.3	33.5	24.4	19.5
District of Columbia	34.9	33.5	33.5	35.2	38.0	29.1
Virginia	23.5	20.1	22.5	19.9	25.9	20.7
West Virginia	21.6	17.4	21.0	17.0	32.6	22.9
North Carolina	20.0	14.2	20.2	14.8	19.1	12.6
South Carolina	18.7	12.6	20.8	14.4	15.7	10.2
Georgia	15.5	12.2	16.8	13.8	12.6	9.1
Florida	20.1	19.6	19.6	21.2	19.7	15.3
East South Central						
Kentucky	16.9	15.7	16.5	15.2	21.2	21.9
Tennessee	16.4	14.2	14.9	13.0	22.7	20.0
Alabama	15.9	12.2	16.0	12.4	15.6	11.7
Mississippi	16.9	13.4	17.8	14.9	16.1	11.8
West South Central						
Arkansas	12.4	10.5	12.9	11.1	10.3	8.5
Louisiana	22.4	17.5	24.2	19.2	18.8	14.4
Oklahoma	16.0	14.4	15.7	14.3	19.0	15.5
Texas	17.2	14.4	16.9	14.3	18.6	14.9
Mountain						
Montana	19.3	19.3	19.7	19.3	†	†
Idaho	19.0	17.5	19.3	17.7	0	0
Wyoming	20.1	16.4	19.6	15.8	†	†
Colorado	16.4	17.8	16.5	17.9	†	†
New Mexico	12.1	8.3	12.7	8.7	†	†
Arizona	14.3	11.0	14.1	11.0	†	†
Utah	23.4	19.4	23.7	19.7	0	0
Nevada	21.0	20.9	20.7	20.2	†	†
Pacific						
Washington	21.9	26.1	21.8	26.1	†	†
Oregon	21.6	25.9	21.6	25.9	†	†
California	21.2	24.7	21.1	25.0	22.7	18.0

\*Adjusted on basis of age distribution of the total population of the United States enumerated in 1940

†Less than 10 deaths

Persons with a blood sugar below the screening level and no glycosuria were notified that the tests revealed no laboratory evidence of diabetes. If glycosuria with or without a blood sugar above the screening level was encountered, a further test of urine and blood was given. Dextrose tolerance tests were performed if previous tests of blood and urine

were examined to permit direct comparison, which demonstrated a difference of 20 mg between average venous and capillary blood sugar level.

The ratio of cases of diabetes to the portion of population tested revealed that there were 40 diabetic persons in Oxford under treatment and 30 more cases of the disease discovered, which represents an

incidence of 0.8 per cent known and 0.6 per cent newly discovered cases, or a total incidence of 1.4 per cent for the 4983 inhabitants. Since 29.4 per cent of the townspeople were not reached by the testing program, it is estimated that the number of previously undiscovered cases of diabetes might have risen to 47 had all the townspeople been tested. The 40 known cases in addition to these 47 estimated cases would be equivalent to 1.7 per cent of the population of the town.

The early discovery of diabetes may be considered a form of preventive medicine, because it is generally agreed that the case detected early does the best. Statistics of diabetes discovered by life-insurance examination and of the disease in the medical profession and in the Army, as well as the opinions of doctors intimately concerned with treatment, attest this idea.

This survey is of great importance. It has set a new standard for estimates of the prevalence of diabetes. If the data obtained are duplicated and hold for the country as a whole, the implication would be that instead of 1,000,000 diabetic persons in the United States there are actually 2,000,000. The million *unknown* cases would on the whole be the ones most amenable to treatment, because the majority would be the mild, symptomless cases and those of recent onset, by all standards presenting the best prognosis, but at the same time probably of a lower income group, thus necessitating special provisions for treatment. Moreover they constitute the group *par excellence* for possible obtaining of life insurance and thus may arouse the interest of life-insurance companies — greatly to the advantage of the diabetes situation. On the other hand, one must remember that a small percentage of unrecognized diabetic cases are severe, because the knowledge of the diabetes is first disclosed after entrance to the hospital in diabetic coma. Thus, of 10 patients representing nine decades of life, shown by Joslin in Indianapolis in late 1946, none knew they had the disease until advised of the fact on their recovery from acidosis in the Indianapolis City Hospital. The patients were in the low-income group.

This survey has substantiated the notable and unexpected incidence of diabetes as found among Selective Service registrants by Blotner<sup>2</sup> and by Gates<sup>4</sup> in an industrial establishment.

In a comprehensive discussion of recent studies on diabetes and diabetic patients, Herbert H. Marks,<sup>5</sup> of the Statistical Department of the Metropolitan Life Insurance Company, arrives at the conclusion that the number of *known* cases in the United States is in the neighborhood of 700,000. In any comparison of Mr. Marks's estimate with other estimates, one should bear in mind that figures larger than this include some unknown as well as known cases. He believes that there are 55,000 new cases annually, thus raising his estimate by 5000 since 1946.<sup>6</sup> Approximately 4,125,000, or 2.9 per

cent of the population (2.1 per cent of the males and 3.8 per cent of the females), he considers, will become diabetic before they die. The highest rates are in the urbanized industrial states in the northeast section of the country and the lowest in the southern states and the southwest. Where the Negro population is urbanized and has access to abundant medical and health service, their diabetic death rates are high. For the country as a whole, white and Negro age-adjusted death rates were more than 50 per cent higher in cities than in rural areas, this was true — and even by more than 100 per cent — for the nonwhite population. In the article by Mr. Marks is a table for each state in the

TABLE 3 *Death Rates from Diabetes Mellitus in Various Countries 1938\**

COUNTRY	DEATH RATE per 100,000	COUNTRY	DEATH RATE per 100,000
United States	23.9	Belgium	19.7†
Canada	13.8	France	10.1†
Argentina	7.0†	Italy	10.5
Uruguay	5.7†	Spain	9.4†
Chile	4.6†	Portugal	6.2†
Ireland and Wales	11.5	Lithuania	3.7†
Scotland	17.2	Estonia	3.0†
Northern Ireland	12.9	Czechoslovakia	12.3†
Irish Free State	9.2	Hungary	6.1†
Norway	9.0	Bulgaria	7.8†
Sweden	10.8	Roumania	3.0†
Denmark	20.4	Greece	4.9
Finland	8.1	Australia	17.7
Germany	19.3†	New Zealand	18.8
Austria	12.2†	Union of South Africa	13.5
Switzerland	15.4†	Japan	4.2
Netherlands	14.5		

\*Adapted from Marks.<sup>5</sup>

†1937

†1936

†1934

†1935

country, showing crude and age-adjusted diabetes death rates per 100,000 whites and nonwhites separately for 1940 (Table 2).

To Mr. Marks we are also indebted for Table 3, which gives the death rates per 100,000 for diabetes mellitus in various countries of the world for the year 1938. The high rates for the United States and Denmark are significant. It is difficult to understand why England and Wales, Norway, Sweden, Finland and the Netherlands have such low mortalities — 14.0 per 100,000, provisional for 1939 — compared with the neighboring countries of Denmark and Belgium.

The experience of the Metropolitan Life Insurance Company since 1911 shows a steady increase in the crude death rates from diabetes to a maximum in 1940. Since then, the rate has fallen rather rapidly, with the 1945 rate the lowest since 1938. A notable feature of the trend in mortality is the decline recorded during the recent war years. The experience of England shows that "at the low point in 1945, the English death rate from diabetes was more than 25 per cent under the peak of 1940, and more than 20 per cent under the average for 1935-1938."

It would appear that a significant part of the reduction in diabetes mortality recorded in the two wars is genuine and that restrictions on food supply are a factor in this trend. The enforced reduction in food intake tends to ameliorate the condition of many diabetics and also helps to prevent or postpone the onset of the disease in susceptible individuals. In this country, at least, the favorable trend in diabetes during World War II reflects also the absence of serious respiratory epidemics during the entire war period, as well as the success of chemotherapy. This has proved a boon to diabetics not only in combating pneumonia and other infections, but also in the successful management of surgical complications of diabetes. On the other hand, the decline in the diabetes death rate is spurious to some extent in that, with the wartime disruption of medical practices, the reporting of causes of death probably suffered in quality.

The most notable feature of the wartime mortality experience for diabetes is the considerable decline in the death rates in late middle life and old age. The rates in 1944 and 1945 were the lowest in years. However, the recent improvement at the older ages was sufficient to wipe out only a fraction of the long-term increase in the death rates from the disease. Consequently, at ages 65 to 74, the rate in 1941-1945 among males was 34 per cent higher than in the preinsulin years, 1920-1922, and among females it was 81 per cent higher than in 1920-1922.

Statistics on the incidence of diabetes in Mannheim in 1944 were recorded by Oberdisse and Nagel<sup>7</sup> as 190 per 1000 population as compared with 213 for Bavaria and 229 for the whole of Germany. Lombard<sup>1</sup> computed a mortality rate of 5 per 1000 as representing the situation in 1947 in Massachusetts.

A series of patients admitted to the Central Hospital, Borås, Sweden, between 1932 and 1941 have been analyzed and reported by Dahlberg and Grill.<sup>8</sup> At the conclusion of the period a follow-up study showed that 515 patients (66 per cent) were alive, 240 (30.8 per cent) dead and 24 (3.2 per cent) untraced, making a total of 779 cases. Female patients predominated—55.8 per cent of the living and 60.7 per cent of the dead.

An attempt was made to compare the first five years, in which the calculated low-carbohydrate Petrén diet was employed, with the second five years, in which the normal diet was given, but the writers properly point out that the small number of cases and various extraneous factors enter into such a comparison. In the second five years the daily diet varied in carbohydrate between 296 and 369 gm, in protein between 91 and 151 gm, in fat between 94 and 120 gm, and in calories between 2605 and 3127 for individual days. It is evident that the percentage of patients admitted on account of diabetes was less in the second than in the first period, and, correspondingly, the percentage admitted on account of other diseases was greater in the second than in the first period. The fact that insulin was given to 52.5 per cent of patients admitted in the first five years, compared with 74.2 per cent in the second five years, must be considered in any evaluation of the two types of treatment. The cost of insulin purchased by the Central Hospital of Borås for patients treated in the Hospital was 2839 kroner for the first five

years and 6421 kroner for the second five years. Hypoglycemia was present in 5 cases in the first period and in 28 in the second, also showing the greater use of insulin. The average stay was twenty-four days in the first group and twelve days in the second. Coma and pre-coma occurred nearly half less often in the second than in the first period, but here again the influence of insulin and not the diet alone must be taken into account.

Of the 240 deaths, cardiovascular disease accounted for 50 per cent, general and local infections for 16 per cent, and diabetic coma for 5 per cent. Of the 12 deaths from coma, 11 were in females, and the authors state "that these figures indicate a sex difference in resistance to ketone formation." On the other hand, one might compare the 28 deaths from diabetic coma in the Joslin group treated at the New England Deaconess Hospital during a similar period, of whom 8 were males and 20 were females, and the mortality 6 per cent among the males and 9 per cent among the females. The Borås cases, like the Joslin series, show an increasing mortality from coma when it occurs in older people. Their total mortality from diabetic coma in their follow-up was 5 per cent as compared with 3.1 per cent in a follow-up of 651 deaths in the Joslin group for January 1, 1944 to May 15, 1946. The diagnosis "diabetes," which was reported especially in older people, was 10 per cent, and that of tumors was 7 per cent, with 16 deaths from miscellaneous causes. The authors conclude that the probable mortality among diabetic persons is three times as great as that of the general population.

The year 1948 completes my fifty years of practice of medicine and active interest in diabetes. The results of treatment of the cases coming under my supervision and that of my associates under the auspices of the George F. Baker Clinic in Boston were recently published in the Statistical Bulletin of the Metropolitan Life Insurance Company.<sup>9</sup> All my cases, anonymously by number, have been summarized on cards, and the statistical studies have been carried out in the Statistical Bureau of the Metropolitan Life Insurance Company. For the preparation of these statistics 99 per cent of the patients treated since 1898 have been traced, largely as a result of the courtesy of the medical profession in responding to requests for information. The death rates (Table 4) and the increasing longevity of diabetic patients (Fig. 1) give ground for encouragement.

Both the table of mortality and the chart of life expectancy agree in showing that in each successive period of treatment for all ages there has been absolute uniformity in that the results have been steadily improving for each succeeding epoch. The following quotation is illustrative:

At the younger ages these reductions were nothing less than spectacular. Thus at age 10, the death rate in 1922-1925 was 84 per cent less than in the period 1914-1922.

Further sharp gains have been made at every age down to the present, and as before these have been relatively greatest at the younger ages. Thus, even between 1929-1938 and 1939-1945 the most recent of the periods into which the data are divided for comparison, the death rate at age 10 showed a decline of 43 per cent, and at most ages under 45 the reduction between these two recent periods exceeded 30 per cent.

When the rates in the most recent years, 1939 to 1945 are compared with those prevailing before insulin, the revolution in the outlook for diabetics is even more sharply

life at the selected ages of 10, 30, and 50 years in successive periods before and since the discovery of insulin. Prior to 1914 the average 10-year-old diabetic child lived a little more than a year, and during 1914-1922 the expectation of life at age 10 was only a little higher — about 2½ years. The first years of insulin, 1922-1925, saw a gain of nearly 12 years, and marked increases have been recorded in every successive period. Even the most recent period, 1939-1945, shows a gain of a little more than 5 years in the expectation of life at this age over 1929-1938. Today with an expectation of life of 45 years, the average diabetic

TABLE 4 Death Rates among Diabetic Patients in 1897-1945 according to Experience at George F. Baker Clinic\*

Age	DEATH RATES†					
	1897-1913‡ per 100,000	1914-1922‡ per 100,000	1922-1925‡ per 100,000	1926-1928‡ per 100,000	1929-1938‡ per 100,000	1939-1945‡ per 100,000
yr						
10	824.0	386.1	61.4	19.1	8.1	4.6
15	623.0	398.8	84.0	14.9	9.2	5.6
20	614.0	410.8	89.4	18.3	12.6	7.6
25	585.6	342.8	77.4	28.0	15.9	10.1
30	359.8	216.8	74.8	33.4	13.9	9.8
35	200.6	152.1	57.5	28.5	10.6	9.4
40	165.7	115.1	34.7	23.8	16.6	10.4
45	119.8	87.1	33.4	26.3	22.2	15.2
50	96.1	77.4	45.3	41.0	30.6	24.3
55	97.1	90.1	64.2	46.5	46.4	36.4
60	188.8	112.5	85.2	70.1	66.6	52.4

\*Adapted from Statistical Bulletin Metropolitan Life Insurance Company.

†Excludes deaths within one week of admission or hospital discharge.

‡Preliminary data.

§Insulin era.

defined. At age 10, the recent rate is 99 per cent less than in 1914-1922. Reductions of 95 per cent or more are found at all ages up to 30 and of 90 per cent to 95 per cent at ages 30 to 40. Even at age 60, the highest age shown in

child of 10 in this experience may expect to reach his 55th birthday.

Analysis of the causes of death among diabetics in this experience shows further what insulin and other advances

### Experience of George F. Baker Clinic, Boston Massachusetts 1897 to 1945

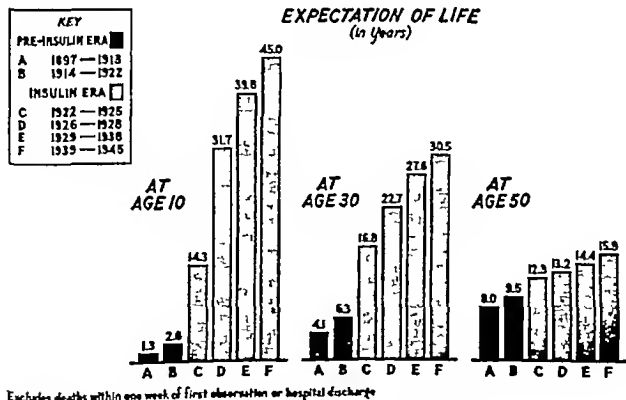


FIGURE 1 Increasing Longevity of Diabetic Patients (Reproduced from Statistical Bulletin Metropolitan Life Insurance Company\* by Permission of the Publishers)

the table the rate in 1939-1945 was 53 per cent less than in 1914-1922.

Figures for expectation of life of diabetics computed from the mortality rates observed among these patients of the George F. Baker Clinic likewise attest the very great improvement in the outlook for persons with the disease. The chart on page 7 shows the expectation of

in the treatment of diabetes have accomplished. Before insulin diabetic coma snuffed out the lives of practically every diabetic child and of many diabetic adults. The death rate in recent years from this cause is 99 per cent less than in pre-insulin days. The mortality from gangrene, which was a frequent cause of death of diabetics in earlier years, has been reduced nearly 60 per cent. The mortality

from infections, to which diabetics are particularly susceptible and which in pre-insulin days were highly fatal, has likewise been cut radically the death rate from pneumonia to one sixth of the pre-insulin rate, and from tuberculosis to one eighth.

The chief causes of death which show little or no reduction in mortality are the cardiovascular-renal diseases and cancer, but this is not surprising in view of the similar trends in the general population and in view of the in-

992, or 13 per cent of the total. The authors compared the mortality experience among diabetic patients of the Mayo Clinic with that of white persons of the general population in 1930, the approximate mid-point of this experience.

Table 5 shows the death rates per 1000 by age in this experience by ten-year age groups. The death

TABLE 5 *Annual Death Rates among Diabetic Patients of the Mayo Clinic (1923-1938, with Patients Traced to 1940)*

AGE INTERVAL yr	ALL CASES			CASES WITH NO ASSOCIATED DISEASES		
	PERSON-YEARS IN INTERVAL	DEATHS IN INTERVAL	ANNUAL DEATH RATE per 1000	PERSON-YEARS IN INTERVAL	DEATHS IN INTERVAL	ANNUAL DEATH RATE per 1000
Under 10	479	4	8.4	297	3	10.1
10-19	1873	30	16.0	968	16	16.5
20-29	2531	27	10.7	1074	11	10.2
30-39	3839	70	18.2	1084	12	11.1
40-49	7248	177	24.4	1168	16	13.7
50-59	12944	496	38.3	1326	38	28.7
60-69	12717	927	72.9	1211	59	48.7
70-79	4668	557	119.3	336	45	133.9
80 and over	491	86	175.2	16	1	64.5
Totals	46790	2374	50.7	7480	201	26.9
Mean death rate standardized*			25.2			19.5

\*Standardized on the basis of age distribution of white persons in the United States, 1930.

creasing average age of the diabetic patients in this experience.

Despite the very satisfactory improvement in the prognosis for diabetics demonstrated by this experience, further substantial gains can be achieved. The length of life of patients in this experience is, at every age, still about one fourth less than that of the general population.

Berkson, Gage, and Wilder<sup>10</sup> have made life tables for diabetic patients based upon the experience of patients observed at the Mayo Clinic between 1923

TABLE 6 *Life Expectancy of Diabetic Patients of the Mayo Clinic Compared with that of the General Population by Sex and Age (1923-1938, with Patients Traced to 1940)*

AGE	LIFE EXPECTANCY* OF DIABETIC PATIENTS OF MAYO CLINIC			LIFE EXPECTANCY* OF WHITE PERSONS, UNITED STATES 1930
	BOTH SEXES	MALES	FEMALES	
yr				
10	37.8	37.4	38.3	56.6
20	33.6	32.3	35.3	47.1
30	26.8	25.3	28.6	38.6
40	21.3	20.1	22.8	30.2
50	15.6	14.9	16.3	22.3
60	10.5	10.4	10.6	15.3
70	7.2	7.0	7.3	9.5

\*Expectancy for diabetic patients calculated by method of Reed and Merrell for constructing an abridged life table.

and 1938 and traced, for the most part, through 1940. The authors included all patients diagnosed as diabetic except those who at the original observation also had a malignant neoplasm. Their series consists of 7408 patients, most of them residents of the middle West. Unlike most clinical series, male patients outnumbered female. The proportion of children was unusually small. In addition to the main group a separate analysis was made of cases free of "associated diseases", this group numbered

rates are at their lowest level at the childhood and early-adult ages, and rise sharply after the age of forty. The yearly death rate at all ages for the total experience adjusted to the age distribution of white persons in the general population in 1930 was 25.2 per 1000. This is approximately two and a half times the death rate for the white population of the country in 1930. For cases free of "associated diseases," the rate was 19.5, or nearly twice the figure for the general population. The rate for females was about 10 per cent less than that for males, in the general population in 1930 the difference was 16 per cent. The comparison with the general population is more favorable at the older than at the younger ages. At most ages under forty, the death rates among the diabetic persons were more than three times as high as the 1930 figure for the general population, between ages ten and twenty, they were more than seven times as high.

Figures on expectation of life computed from the mortality rates observed are shown in Table 6 and the corresponding figures for white persons in the general population in 1930. At age ten, the expectation of life for diabetic patients in the Mayo Clinic experience was 37.8 years as compared with 56.6 years in the general population. The figures decline steadily with age, as do those in the general population. At most ages, the figures for the diabetic patients were about a third less than those for the general population in 1930.

The results of this analysis conform to those reported for patients of the George F. Baker Clinic, although the figures are not strictly comparable, principally because of the difference in the periods

covered in the two experiences. The analysis of the George F Baker Clinic records shows a steady increase in the longevity of diabetic persons since the discovery of insulin.

### DIABETIC ACIDOSIS AND COMA

The essential feature emphasized at the New England Deaconess Hospital and responsible for the improvement in mortality of its cases of coma during the last seven years is the attitude that every case of diabetic acidosis and coma is a grave emergency and that the patient needs intensive study, to determine the diagnosis and especially to determine the complications present, as well as an immediate effort to determine the amount of insulin needed and to give that dose as promptly as possible. Occasional, profoundly unconscious patients may need 500 to 1000 units, and if any less than this dose is given in the first few hours, delay occurs at a time when it is most dangerous. Those who adopt automatic rules by which a patient gets 50 units every thirty minutes may find in the occasional very severe case that in the first two or three hours only a comparatively small amount of insulin has been given and during that time the patient has lost ground.

The striking improvement in the mortality rate of profoundly unconscious patients at the Deaconess Hospital has been due to willingness to give 500 or 1000 units, or even more, in the first two hours of treatment when it is necessary. Thus, whereas 35 per cent of the profoundly unconscious patients died in the period before 1940, since 1940 only 10 per cent have died. Everyone knows that the mortality in the profoundly unconscious patient is higher than that in patients who are not yet completely unconscious. Thus, Nicholson and Branning<sup>11</sup> report a mortality of 64.6 per cent in 55 patients in coma who were profoundly unconscious. When they omitted from this series unconscious patients whose deaths were due to complications other than coma, they still had a mortality of 48.8 per cent. Another striking fact brought out in their article had to do with the use of sodium lactate. Thus, patients who received sodium lactate showed a mortality of 8.5 per cent for those twelve hours in coma, 66.6 per cent for those in coma from twelve to twenty-four hours and 50 per cent for those in coma for twenty-four hours. Patients treated without sodium lactate showed a mortality of 9.1 per cent for those twelve hours in coma, 22.2 per cent for those in coma twelve to twenty-four hours and 66.6 per cent for

3 patients in coma for twenty-four hours. Little advantage was obtained by the use of sodium lactate. They also described 2 cases of diabetic acidosis associated with a decrease in the serum potassium concentration, with recovery in 1.

Shock may occur with coronary occlusion, as in Case 24095 with a fall in the blood carbon dioxide to 20 vol per cent but with no acetone bodies in the blood. Differential diagnosis is therefore important. This case might have been thought to be a death from diabetic coma if there had not been quantitative measurement of the acetone bodies in the blood, which showed less than 2 mg total acetone bodies per 100 cc.

In the treatment for diabetic acidosis of 96 children, Hartman and Ergasian<sup>12</sup> made use of sodium lactate to raise the blood carbon dioxide. The method is summarized by the statement that insulin is immediately administered in amounts of 2 units per kilogram of body weight, and 30 cc of sixth-molar sodium lactate solution per kilogram of body weight is given intravenously. At the same time 40 cc of hypotonic Ringer's solution per kilogram and 30 cc of sixth-molar sodium lactate per kilogram of body weight are given subcutaneously. Six hours later approximately 0.5 unit of insulin per kilogram is administered, and if necessary sixth-molar sodium lactate is given subcutaneously and plasma, concentrated albumin or whole blood as required. Five of the 96 children died, although acidosis was relieved before exitus.

(To be continued)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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### CASE 34121

#### PRESENTATION OF CASE

A sixty-six-year-old housewife entered the hospital with swelling of the right leg

Two weeks prior to admission, following a day of standing at the election polls, swelling of the right leg appeared, with slight aching referred to the hip and lower back. A physician advised bed rest, which resulted in definite improvement during four days' rest, but upon arising the swelling and discomfort returned.

Physical examination revealed a comfortable patient with marked pitting edema of the right leg, extending to the thigh. The extremity was cyanotic and cool, with moderate venous distention and diminished arterial pulsations on that side. A small area of tenderness was found over the calf. Homans's sign was negative. There was also slight edema of the left lower leg. No other abnormal signs were observed.

Examination of the blood disclosed a red-cell count of 4,400,000, with a hemoglobin of 15 gm, and a white-cell count of 5900, with 69 per cent neutrophils, 22 per cent lymphocytes and 9 per cent monocytes. Urinalysis was negative, and the prothrombin time was normal. An x-ray film of the chest was normal.

Following admission heparin and dicumarol therapy were instituted, and the patient was maintained with a prothrombin time of 40 to 60 seconds (control, 18 seconds) for about two weeks, following which she was allowed up with a constricting dressing on the right leg. During this period the temperature occasionally reached 99°F, and she complained of vague pain in the upper lumbar area. An intravenous pyelogram showed the right kidney to be displaced to the right by a mass that extended 5 cm to the right of the lumbar spine. A barium enema revealed an abnormality of contour having the appearance of extrinsic pressure just distal to the hepatic flexure, which was moderately displaced. A gastrointestinal series showed the duodenum to be quite definitely displaced, principally anteriorly, but also slightly to the left. A diver-

ticulum extended from the second portion of the duodenum. No other contributory findings were discovered by x-ray examination.

About four weeks following admission, an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR HORATIO A ROGERS I am sure that I should see the x-ray films before I go any farther.

DR STANLEY M WYMAN The lung fields appear clear. The heart shadow is not remarkable. There are no visible mediastinal or hilar masses. The film of the abdomen shows dye in the right urinary passages and a smooth, somewhat spindle-shaped mass extending to the right of the spine, compressing the upper pole of the kidney on the right and displacing it laterally. This is well seen in the oblique view. There is no unusual area of calcification. There are no other visible masses in the abdomen. The liver and spleen do not appear remarkable. The displacement of the colon is seen here, with the suggestion of an extrinsic pressure defect in the proximal transverse colon. The duodenum is displaced considerably anteriorly in this film, but one cannot outline the mass well.

DR ROGERS The finding of edema of the leg without previous symptoms is in favor of a local rather than a systemic cause of swelling. Direct pressure or venous thrombosis could account for the swelling of one leg and the partial swelling of the other leg only if it involved both right and left branches of the bifurcation of the vena cava, which would make the thrombosis or pressure area quite low down in the vena cava. The swelling is not suggestive of a thrombotic condition arising from the deep veins in the calf because of the absence of Homans's sign, and we do not have to suppose that it was that when we go on and find a mass, which by the organs it displaces must be a retroperitoneal mass in the location where it could partially obstruct the abdominal vena cava and perhaps also cause thrombosis. If all that is true, the question comes down to the nature of this retroperitoneal mass in a sixty-six-year-old woman, which was not immediately fatal and which caused no severe pain and no fever. The absence of fever and the white-cell count enable us to rule out an inflammatory mass fairly well. If it were an abscess in the retroperitoneal region of sufficient size to displace the organs, as it usually does, it would have to be tuberculosis of the spine, and it is unlikely that the spine would not show some evidence of erosion. So I think we can dismiss that possibility.

If it were a retroperitoneal hemorrhage, we would expect a somewhat lower hemoglobin level and red-cell count and severer pain at the time the hemorrhage occurred. Also, it would have to be a very extensive hemorrhage to form a retroperitoneal hematoma large enough to displace the organs as described. If it were a cyst of that size, it would

almost have to be one of either the kidney or the ovary, and we would expect mention of its being felt on abdominal examination.

That brings us down to neoplasm in the retroperitoneal space as the most likely possibility. Can we go farther and try to guess the nature of the retroperitoneal neoplasm? Sixty-six is definitely in the cancer age, which means less and less as people see malignant tumors in all age groups, but the fact remains that there is a higher incidence in elderly people than in young people. Is there any kind of carcinoma that this could have been? It is very unlikely. There is nothing to make one think of the gastrointestinal tract or the ureter, and I think that we will have to say that it was not a primary cancer in the retroperitoneal space. It was presumably not metastatic cancer in the retroperitoneal space because there were no previous symptoms to suggest the existence of a primary carcinoma, and such a huge metastatic mass would be strange without an obvious explanation for its presence. So it must have been some kind of neoplasm of the sarcoma or lymphoma or lymphosarcoma type, if it was a neoplasm. There is a condition (retroperitoneal lipoma) that I have never seen and that is found in middle-aged people, women more than men, and often contains areas of cancer and sometimes areas of hemorrhage. It becomes very large, and it would be capable of producing this picture, I think. It could be a retroperitoneal sarcoma of almost any type, or it could be a retroperitoneal lymphosarcoma. This patient's age is not against that, and we have no way of knowing which it was but so long as I am quite likely to be wrong anyhow, I think I shall guess that it was a rare disease and say that this woman had a retroperitoneal lipoma with thrombosis of the veins producing edema of the right leg.

DR CLAUDE E. WELCH: May I ask Dr. Rogers if he would have operated on the patient?

DR. ROGERS: I am ashamed to say that I did not consider that point in studying the protocol. The patient was apparently getting better, and although no diagnosis was possible without operation, I should think it was very questionable how much operation could accomplish in the way of permanent cure. I probably would have to operate to make the diagnosis but would not be hopeful of curing her. Perhaps a course of x-ray treatment would have helped rule lymphosarcoma in or out without operation.

DR. ROBERT R. LINTON: I should like to say a word about the edema of the right leg. I doubt whether the tumor caused the swelling of the right leg because a tumor mass pressing on the inferior vena cava should cause the left leg to swell also. The unilateral edema suggests to me a deep venous thrombosis of the right leg.

DR. WYMAN: From the x-ray point of view a lipoma might be expected in most cases to show rarefaction. Not necessarily, of course, but that

might be a lead against lipoma. This lesion looked homogeneous in density.

## CLINICAL DIAGNOSIS

Retroperitoneal sarcoma

DR. ROGERS'S DIAGNOSES

Retroperitoneal lipoma

Venous thrombosis

## ANATOMICAL DIAGNOSIS

*Malignant lymphoma, lymphoblastic type*

## PATHOLOGICAL DISCUSSION

DR. WELCH: It is an interesting point that Dr. Linton made. We see 3 or 4 patients each year with thrombophlebitis in the extremities as the first sign of abdominal cancer, and we were interested to discover whether or not there was direct involvement of the vena cava in this case to account for the thrombosis. We operated with a diagnosis of retroperitoneal sarcoma. A long transverse incision was made, and we found, as the x-ray film has shown, the kidney displaced downward and laterally. The large tumor was intimately adherent to the vena cava, which was not thrombosed. We suspected the histologic nature of the tumor as we palpated it and proceeded with the excision of the tumor mass. Other small but definitely enlarged lymph nodes were noted about the celiac axis.

DR. TRACY B. MALLORY: The tumor that we received in the laboratory showed a malignant lymphoma of relatively undifferentiated character, which we diagnosed as lymphoblastic lymphoma. Following operation the patient made a smooth convalescence and is now undergoing x-ray therapy.

DR. LINTON: How large was the mass?

DR. WELCH: I should say 11 by 7 by 6 cm.

DR. ROGERS: Do you think that standing on her feet for such a long period was the cause of the episode of edema?

DR. WELCH: We thought that it was.

DR. ROGERS: Was the mass movable with changes of gravity?

DR. WELCH: No, it was firmly fixed.

## CASE 34122

### PRESENTATION OF CASE

A sixty-nine-year-old watchman entered the Emergency Ward because of difficulty in voiding of two months' duration.

During this period repeated instrumentation and catheterization were required, and blood clots were passed in the urine from time to time. Voiding was difficult, delayed and in small amounts. Episodes of epigastric pain followed by vomiting were reported, but the history was vague and erratic. Bowel habits were normal and without diarrhea or melena.



A 40-pound weight loss in the six months before entry was reported

Physical examination revealed an emaciated, pale, drowsy, chronically ill man, with a hot, dry, wrinkled skin. The heart and lungs were not remarkable except for a few extrasystoles. The abdomen was scaphoid and difficult to palpate, some resistance was encountered in the right upper quadrant, but no tenderness, mass or liver edge could be made out. Rectal examination was negative, the prostate was of normal size, with a slightly granular consistence. The left scrotum was enlarged four or five times normal.

The temperature was 101.2°F, the pulse 80, and the respirations 18. The blood pressure was 105 systolic, 60 diastolic.

Examination of the blood revealed a red-cell count of 3,800,000, with a hemoglobin of 8.5 gm, and a white-cell count of 8200. A stool examination showed a ++++ guaiac reaction, and the vomitus a ++ guaiac reaction. Urinalysis disclosed a +++ test for albumin, with numerous red cells and occasional white cells in the sediment. The non-protein nitrogen of the blood was 45 mg per 100 cc, the total protein 5.6 gm, the fasting blood sugar 96 mg, the calcium 7.6 mg and the phosphorus 2.6 mg per 100 cc. The chloride was 100 milliequiv per liter, and a van den Bergh reaction was normal. The amylase was 38 units per 100 cc, and the alkaline phosphatase 3.8 units. An intravenous pyelogram showed right-sided calyceal blunting without ureteral dilatation, this was later confirmed by a retrograde pyelogram, with the demonstration of a bladder stone. Chest films and a barium enema were not remarkable. A gastrointestinal series demonstrated an obstruction at the antrum, with an area of marked narrowing 3 cm in length, but a normal-appearing duodenal bulb was seen. Cystoscopy revealed moderate trabeculation and a 2 cm oval, granular, whitish stone on the bladder floor, no tumor was seen.

After completion of studies it was agreed that the patient should be prepared for surgical exploration. On the fifth hospital day, however, he developed sudden, severe, nonradiating, right-lower-quadrant and right-upper-abdominal pain, with associated physical findings of lower-abdominal distention, tympany, rumbling peristaltic rushes and marked deep right-lower-quadrant tenderness, there was no spasm or rebound tenderness. Impacted barium was removed from the rectum, with slight relief. An upright abdominal film showed no subdiaphragmatic air and no dilated loops of bowel. A Levine tube was passed, and the patient vomited 1500 cc of brown watery fluid, which was equivocal on guaiac test. The symptoms subsided gradually, and parenteral fluid therapy was again directed toward surgical preparation. Two days later he had a similar sudden, severe episode, with the same findings and

another normal abdominal film. Relief was again obtained by aspiration of gas and 500 cc of fluid from the stomach.

An operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR ROBERT R. LINTON: As one reads the record, this patient obviously had something much more seriously wrong with him than the genitourinary condition when he came to the Emergency Ward. He had difficulty in voiding of two months' duration. I believe, however, that that had very little to do with the condition for which I am supposed to discuss this case. Obviously, he had a bladder stone, and I assume that that and perhaps some obstruction from the prostate were the reasons for the difficulty in voiding. In addition, he had a mass in the left side of the scrotum due to a large scrotal hernia or hydrocele, probably the latter. These, I think, are unrelated, although it is possible that if it were a hernia, one could connect the episode described later on with an incarceration and perhaps partial obstruction of the small intestine. It is interesting that very little vomiting is mentioned during the hospital admission, and yet the vomitus is reported guaiac positive. It is also significant that the stool examination showed a ++++ guaiac reaction. Those findings suggest that he was suffering from some lesion in the gastrointestinal tract that had produced blood in the stools. The x-ray examination, I think, reveals the source of bleeding, both in the stools and in the vomitus. Before going farther we might see the x-ray films.

DR STANLEY M. WYMAN: The chest appears within normal limits for a patient of this age. The lesion described in the gastrointestinal tract is seen in the region of the antrum and prepyloric region on these two films and is well seen on these two spot films. There seems to be a constant narrowing that does not change in contour. There is a suggestion of a normal mucosal pattern, but that is not definite. The point about the films that interests me is this irregularity in the upper second portion of the duodenum, which is not mentioned in the record. It is a constant finding on all the films, and there seems to be a suggestion of shelf formation distally and possibly proximally on the lesser curvature. On the medial aspect of the duodenum there is an accumulation of barium that may be in a diverticulum or an ulcer crater. I do not see the duodenal cap adequately outlined on any film. I cannot comment further on that. This brings up the question whether or not there were one or two lesions in the upper gastrointestinal tract. The colon shows nothing remarkable. A film from the pyelogram shows a stone in the bladder. I think the blunting of the calyces on the right is minimal. The left kidney is displaced downward, but I do not know why.

DR LINTON Do you know anything about the six-hour or twenty-four-hour film? Was there any gastric residue?

DR WYMAN That is not included in the series of films that I have here

DR LINTON It is certain that one has to take the roentgenologist's opinion of this finding as showing evidence of a lesion in the distal end of the stomach and a questionable lesion apparently in the second portion of the duodenum. Would you say that the duodenal loop is widened at all?

DR WYMAN No, there is no widening

DR LINTON I ask that because a wide duodenal loop frequently means a malignant or inflammatory lesion involving the pancreas

We do not know too much about what happened during the stay in the hospital except that operation was decided on. The patient suddenly developed upper abdominal pain, lower abdominal distention and rumbling peristaltic rushes, and when a Levine tube was passed down the stomach he vomited 1500 cc of brownish watery fluid. I assume that he must have aspirated some fluid as well as this large amount that he vomited. One-and-a-half liters is considerable residue in anyone's stomach — especially one who is not taking a great deal of nourishment by mouth. The episode apparently repeated itself, and again 500 cc was aspirated.

It seems to me that the diagnosis in this case is very obvious, and for that reason I am probably wrong. We are dealing with a patient who has a lesion in the pyloric end of the stomach, which constricted the lumen sufficiently to cause dilatation of the stomach with retention of gastric secretions and food taken by mouth. I have ruled out small-bowel obstruction since the small bowel was not dilated. As a matter of fact, when I was a resident here (in the days before the Levine tube was used routinely) I helped one of the visiting men operate on a patient for small-bowel obstruction because of large peristaltic waves seen in the right lower quadrant, and much to our amazement the patient had acute dilatation of the stomach and no small-bowel obstruction whatever. The patient responded very well to simple lavage and drainage of the stomach. It is my opinion that the patient in the case under discussion had a lesion of the distal portion of the stomach involving the pyloric end, which, in view of the positive guaiac test on the stool and vomitus, suggests a malignant lesion. I am unable to rule out or in a lesion involving the second portion of the duodenum, but in view of the fact that we have no evidence in the x-ray report that there is marked constriction in the duodenum, I believe that the lesion is more likely to be in the distal end of the stomach. My diagnosis is carcinoma of the pyloric end of the stomach, with pyloric obstruction.

DR ALFRED KRANES If there were a lesion in the second portion of the duodenum, would you consider anything else?

DR LINTON One would have to consider carcinoma of the head of the pancreas, which is unusual without some evidence of jaundice due to obstruction of the common bile ducts.

DR KRANES I was thinking of lymphoma with multiple lesions, if that observation is correct.

DR LINTON That is a good suggestion. I had not thought of a lymphoma here. Malignant lesions of the distal end of the stomach would probably cover it.

DR WYMAN I am at a disadvantage because the examination is not complete. Benign ulcer of the duodenum could produce this picture in the duodenum, and there might have been an ulcer of the prepyloric region that had resulted in scarring.

DR LINTON The fact that the stool gave a + + + + guaiac reaction is a little against a duodenal ulcer due to cicatricial contraction, because such patients do not bleed much, but again the blood could have arisen from the mucosa of the dilated stomach.

DR WYMAN If the duodenal lesion has a crater, with associated spasm, the bleeding is possibly explained.

DR LINTON Yes

#### CLINICAL DIAGNOSIS

Carcinoma of stomach

#### DR LINTON'S DIAGNOSIS

Carcinoma of pyloric end of stomach

#### ANATOMICAL DIAGNOSES

*Duodenal ulcer, active*

*Chronic gastritis*

#### PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY This patient was explored, and a very large, old, indurated ulcer was found in the second portion of the duodenum on the posterior wall. A subtotal gastric resection was performed, and no lesion was found in the stomach other than a mild hypertrophic gastritis. Following operation attention was finally drawn to the complaint for which he came in. The bladder stone was duly crushed and removed, and a small amount of prostatic tissue around the mouth of the bladder was removed. After multiple operations the patient went home with a good recovery.

DR KRANES What was the cause of the right-lower-quadrant pain?

DR MALLORY Acute gastric dilatation, so far as we know — nothing else was found.

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## DIABETES — A MASS EXPERIMENT IN THE STUDY OF ARTERIOSCLEROSIS

Two papers on diabetes in this issue of the *Journal* bear witness to the continuing importance of the disease despite the advances that have been made in its control. The diabetic group furnishes, in particular, an unusual group for the study of the degenerative diseases, for although its members live on the average for fourteen years after the diagnosis is made, 67 out of 100 succumb to hardening of the arteries. We may expect, therefore, from recent evidence,\* that the degenerative changes of old age should be further deferred and life prolonged beyond the present sixty-four years by an organized and

intelligent study of this group, employing the most modern methods.

The bounds of the experiment are definite. Here is a homogeneous group of 1,000,000 patients with known and 1,000,000 persons with undiagnosed diabetes, two thirds dying of arteriosclerosis with the average duration of their diabetes now fourteen years, and their average age at death sixty-four years. The extension of any one of these frontiers is an achievement dependent upon the individual efforts of both patient and doctor. Like the athlete and his trainer, success will be found where the partnership between the two has been the closest.

The data already obtained in this mass experiment show its importance. How is it that coronary thrombosis is eight times as frequent in diabetic as in nondiabetic women? Why are calcified pelvic arteries found in 46 per cent of 79 young persons who have had diabetes for twenty or more years with only 1 such case noted in 75 nondiabetic persons of similar age? Of what significance is the demonstration that the chance of obtaining a living child from a pregnant diabetic mother is only 20 per cent if the pelvic arteries are calcified but more than 90 per cent if they are not calcified? Why should 20 cases of calcification of the vas deferens be observed in diabetic patients compared with 1 case in a nondiabetic person?

The participation of endocrinologic factors may be studied since diabetes itself is conditioned by a deficiency of a specific hormone, insulin. Biochemical analyses of humoral factors, of which the lipid cholesterol may be mentioned, are rapidly accumulating. The influence of metabolic and infectious agents is under scrutiny.

The discovery of the cause for the premature advent of degenerative changes of old age in a person with diabetes will have far-reaching consequence for the whole human race.

## THE GENERAL PRACTITIONER ORGANIZES

THE general practitioner of medicine, after centuries as the leading exponent of his profession, is at last having efforts made to restore to him some-

\*Diabetes Exhibit, Interim Session, American Medical Association January, 5-8, 1948

thing of this position, even in an age of science that seemed to have passed him by

The American Medical Association established a section on general practice in 1946, and in June, 1947, on the occasion of the centennial convention of the Association in Atlantic City, the American Academy of General Practice was founded. The wheel has completed its cycle. Each of the major divisions of medicine that split off from the main body of this art has achieved its special rating and its special privileges, the parent and protector of them all has at last been stirred to seek its own salvation.

There have been organizations of general practitioners before now — to wit, every state medical society and the American Medical Association itself, a hundred years ago. This is the first time, however, that general practice has raised its voice to be heard throughout the nation, as distinct from the voices of its offspring — perhaps in self-protection against those lesser, if more sparkling, satellites.

The purposes of the Academy as avowed in its constitution are praiseworthy: to promote and maintain high standards of the general practice of medicine and surgery, to encourage and assist young men and women in preparing, qualifying and establishing themselves in general practice, to preserve the right of the general practitioner to engage in medical and surgical procedure for which he is qualified by training and experience, to assist in providing postgraduate study courses for general practitioners, and to encourage and assist practicing physicians in participating in such training.

To be eligible for membership a physician must be engaged in general practice, he must be licensed in the state in which he practices, he must be of the usual high moral and professional character. He must have had at least one year of rotating internship at an approved hospital or the equivalent in postgraduate training, and he must have been in general practice for at least three years.

This new organization of general practitioners is not novel, nor are its purposes in any way original, unless we consider it as being quite different in its aim and ideals from the sometime association of physicians who called themselves Asklepiads. Threatened groups or groups that wish to extend

their influence have always organized, and organization is as old as the family, the tribe or the pack.

The general practitioner, hardy and independent as he is, has had his livelihood threatened by better organized minorities. He has been passed by, over-ridden and denied the privileges of those certified by boards and has found access to hospitals difficult. Organization for self-protection and *self-improvement* has been necessary. In this organization, however, he does not wish to be patronized, and he does not need to be flattered. He knows his worth to the community, and if the community does not know it, it can be taught.

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## NEGRO HEALTH WEEK

NATIONAL Negro Health Week has been planned for April 4 to 11 by the Office of Negro Health Work of the United States Public Health Service. This particular observance is not the result of any recently exploited circumstances, the movement was originated in 1915 by the Negro race's own great leader, Booker T. Washington, whose birthday on April 5 will fall within the designated period.

After Dr. Washington's death the program that he initiated was annually conducted at Tuskegee Institute, at which time Founder's Day was celebrated and the National Medical Association and the John A. Andrew Clinical Society held their meetings. At this time, also, clinics were held at the Institute's John A. Andrew Memorial Hospital, the gift of members of the family of Massachusetts' great abolitionist and Civil War governor. A number of Northern physicians have been guests at these gatherings and have carried away pleasant recollections of the hospitality and courtesy extended to them.

The current health week, while bringing to light some of the problems that confront the Negro, will also, it may be hoped, discover more and more helping hands extended toward him — a greater spirit of co-operation in furthering his adjustment to an environment not originally of his own choosing.

The President's Committee on Civil Rights has recently issued its report proposing 'the enactment by the States of fair health statutes forbidding discrimination and segregation based on race, creed,

color or national origin, in the operation of public health facilities"

This is all very well, and fair laws make fine reading. What is needed, however, is not so much new laws as a new spirit of tolerance and co-operation and understanding. Through all the history of the world there can be found running an unbroken thread of man's humanity to man. When that thread can be broadened into a convincing pattern then may countless thousands cease to mourn.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

FLEMING — Edwin R. Fleming, M.D., of Medford, died on March 4. He was in his sixty-ninth year.

Dr. Fleming received his degree from Jefferson Medical College of Philadelphia in 1904. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow survives.

HEALY — Thomas R. Healy, M.D., of Newburyport, died on February 25. He was in his seventieth year.

Dr. Healy received his degree from Dartmouth Medical School in 1899. During World War I he was chief of the X-Ray Department of the United States Marine Corps and the United States Navy. He was a member of the American Roentgen Ray Society, New England Roentgen Ray Society, Radiological Society of North America and American College of Radiology and was a fellow of the American Medical Association.

A brother, a nephew and a niece survive.

HOWE — Oliver H. Howe, M.D., of Cohasset, died on March 1. He was in his eighty-eighth year.

Dr. Howe received his degree from Harvard Medical School in 1886. He was a former president of Norfolk South District Medical Society.

Four sons survive.

RICE — John Dexter Rice, M.D., of West Boylston, died on October 4. He was in his thirty-third year.

Dr. Rice received his degree from Tufts College Medical School in 1940.

His mother, father, three brothers, a son and two daughters survive.

## A HUNDRED YEARS AGO

The following remarks, by Dr. H. J. Bigelow, of Boston, on a subject first brought to the notice of the profession by himself, in the pages of this *Journal*, are entitled to consideration. He believes that profound narcotism can always be produced by the use of ether or chloroform and that within a short time, no surgeon will commence a formidable or nice operation upon a patient who has not arrived at this stage of *anaesthesia*. When ether is used, inhalation should be of *air impregnated with ether, and passing through it, and not of ether alone*, as from a sheet bag or sac. He has had a good opportunity

of testing the effects of chloroform in his own and other operations, and, indeed, has used no ether since its introduction. It seems to him to be thus far identical with ether in its effects, much stronger and portable, it does not infect the clothes, is less irritating to the lungs, and is at first quite palatable to the patient. In his opinion, it must supersede "ether" of which it is but a variety. — One achievement prepares the way for another and we are again taken by surprise with a new preparation which is to be known under the name of *Collodion* — being a solution of *gun cotton* in ether. Mr. Samuel L. Bigelow, a senior student at the Harvard Medical School informs us that from Dr. Charles T. Jackson he learned the manner of preparing it, for Dr. Jackson had remarked upon it and exhibited specimens before the National History Society, in Dec. 1846 or Jan. 1847, and enumerated various uses to which it might be applied — among others, as a brilliant varnish. For this use Mr. Bigelow soon after prepared a bottle, according to the directions. While engaged in employing it in this way, he accidentally smeared with it a fresh wound on his finger. The smarting called his attention to it, and he endeavored immediately to rub it off. It had dried, however, instantaneously, and remained on. The smarting very soon ceased, and when the film was removed, perfect union had taken place. Since this time, the efficacy of this preparation as a dressing for wounds has been tested, especially those which it is desirable to unite rapidly, by first intention. *Collodion* would seem to possess very eminently, all the requirements for producing such a union. Mr. Bigelow is informed that a series of experiments are being now made at the Mass. General Hospital, by the surgeons in attendance, who will be soon able to test its value and range of application. — Speaking of the Hospital, a copy of the late report of the institution was sent to the editor several days since. From page 10 to 46, the trustees have devoted to the history of the discovery of ether inhalation, and they have taken strong ground, too, in their 4th conclusion, in saying, "The whole agency of Dr. Jackson in this matter appears to consist in his having made certain suggestions, which led Dr. Morton to make the discovery — a discovery which had for some time been the object of his labors and researches." Although drawn up with an air of candor and fairness, this report will be memorable in the series of annual accounts of that beautiful establishment from the circumstance that it bears a history of the ether war. There are no more indications of peace between the rival candidates for favor, than there is between this Government and Mexico. — Another donation of \$100,000 has nearly found its way into the treasury of the institution. At this rate, it will ultimately become immensely rich. Five hundred medical students should be daily learning the details of their profession there. — We take this opportunity to men-

tion, that when a communication is intended for a leading article in this *Journal*, it should be received at the Editor's office not later than Monday of the week preceding that in which the article is to be published. Two pages of each number are left open till Monday morning, which is the latest period for the receipt of brief notices etc. — Extracted from the *Boston Medical and Surgical Journal*, March, 1848

R. F.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### DEPARTMENTAL PUBLICATIONS

The following is a list of publications sent out regularly by the Massachusetts Department of Public Health. They are available to anyone upon request.

*Blood Donor News* (bimonthly) contains news regarding schedules of the mobile unit, collection and distribution of blood, and progress and changes in the program.

*Cancer Bulletin*, a quarterly bulletin for physicians, contains abstracts of important papers on cancer research, diagnosis and treatment.

*Cancer Tidings*, issued bimonthly, is a news letter sent out to members of the co-operative cancer-control committees giving the latest news on cancer-control programs being carried on in the Commonwealth.

*Communicable Disease Information*, sent out weekly, gives up-to-the-minute news of the reported cases of communicable diseases in Massachusetts.

*Contact*, a quarterly bulletin prepared by the Division of Maternal and Child Health containing articles and recommendations on school health work, is primarily directed to school superintendents and school nurses.

*News Letter*, a monthly bulletin, contains articles and news of general interest to all health workers.

*V D Bulletin*, a quarterly for physicians, is designed to disseminate information regarding current advances in the treatment and control of venereal diseases.

### APPOINTMENT OF DR FIUMARA

Dr Nicholas J. Fiumara has been appointed director of the Division of Venereal Diseases of the Massachusetts Department of Public Health, after certification by the Division of Civil Service of the Commonwealth. Dr Fiumara is a graduate of Boston College and Boston University School of Medicine. Since his return from service with the Navy, Dr Fiumara has received the degree of master of public health from the Harvard School of

Public Health. He is a fellow of the Massachusetts Medical Society and the American Medical Association and a member of the Massachusetts Public Health Association and the American Public Health Association.

## MISCELLANY

### NATIONAL HEALTH ASSEMBLY

A National Health Assembly will be held in Washington from May 1 to 4 according to Oscar R. Ewing, federal security administrator. The Assembly is the result of President Truman's message of January 30 requesting the development of national health goals for the next ten years.

The activities of the Assembly in initiating this ambitious program will be largely in the form of panel discussions, each panel to explore fully a specific phase of the health problem. An anticipated contribution of the Assembly will be a clearer picture of how much agreement there is in certain supposedly controversial health fields.

### BELGIUM HONORS DR. RICHARD P. STRONG

The Belgian ambassador, Baron Robert Silvercrux, in an intimate ceremony at Dr. Richard P. Strong's residence on February 7 presented him with the cross of Officer of the Royal Order of the Lion. This award, which had been granted by an executive order of February 24, 1947, was in recognition of the pioneer work that Dr. Strong had performed in 1926 and the following year, when he led a medico-biologic expedition into Liberia and the Belgian Congo.

The Order of the Lion is one of the highest ranking Belgian decorations. It was conferred on Dr. Strong through the offices of the Secretary for Colonies and indicates the high esteem in which he is held in Belgian scientific and colonial circles.

### MARKLE FOUNDATION AWARDS

Among the sixteen scientists appointed as the first group of scholars in Medical Science under the John and Mary R. Markle Foundation plan are Christian B. Anfinsen, Ph.D. (A.B. Swarthmore College, S.M., University of Pennsylvania, Ph.D. Harvard Medical School) to Harvard Medical School in the field of biochemistry; Edward J. Beattie, Jr., M.D. (A.B., Princeton University, M.D. Harvard Medical School) to George Washington University School of Medicine in the fields of surgery and cardiorespiratory physiology; and Henry D. Hoberman, M.D. (A.B. and Ph.D. Columbia University, M.D., Harvard Medical School) to Yale University School of Medicine in the field of biochemistry, particularly in the study of compounds by the use of isotope tracers.

### APPOINTMENT AT COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS

Dr. Otto Lowenstein was recently appointed clinical professor of neurology at Columbia University College of Physicians and Surgeons.

## CORRESPONDENCE

### BILIRUBIN AND THE RENAL FILTER

To the Editor: I have read with great interest Dr. Lawrence E. Young's review "Current Concepts of Jaundice with Particular Reference to Hepatitis" which appeared in the August 14 and 21 issues of the *Journal*. On a single point, however, a fundamental misunderstanding of the facts is put forward in this valuable study.

Dr. Young is of the opinion that the occurrence of bilirubinuria in the different forms of jaundice is explained by the fact that bilirubin-globin—the "indirect" bilirubin,

hemolytic jaundice and retention jaundice — cannot pass the renal filter, whereas the free sodium bilirubinate ("direct" bilirubin) present in the serum of patients with regurgitation jaundice does. This opinion is quite erroneous, for it has long been known that all bilirubin present in serum is bound to the albumin fraction of the serum protein — be it globin or common serum albumin — and consequently does not filtrate or pass by diffusion the kidney membrane or any other semipermeable membrane. This has been shown by dialysis, electrophoresis and ultrafiltration, as pointed out by Snapper and Bendien in their articles entitled "Abtrennung von Serumkolloiden durch Ultrafiltration" (*Acta breo Neerlandica* 1 69-71, 1931) and "On physico-chemical condition of bilirubin in bloodserum and urine" (*Acta med Scandinav* 98 77-82, 1939), by Bennhold in his paper entitled "Über die Viskositätsfunktion der Serumweißkörper" (*Ergebnisse d inn Med* 42 273-375, 1932) and by Pedersen and Waldenström in a study entitled "Studien über das Bilirubin in Blut und Galle mit Hilfe von Elektrophorese und Ultracentrifugierung" (*Ztschr f physiol Chem* 245 152-162, 1937). The results of these investigations are in perfect agreement with the well known facts that cerebrospinal fluid, sweat, saliva, tears and almost all secretions and excretions, with the exception of urine and bile, are free from bilirubin even in long-standing severe jaundice, as demonstrated in the literature cited in my paper "Bilirubin in urine and other secretions apart from the bile and in the cerebrospinal and eye liquors" (*Acta physiol Scandinav* 10 355-365, 1945). Bilirubin is thus a rather singular substance from the point of view of the kidney physiologist, since it is not excreted by filtration in the glomeruli but solely by secretion in the renal tubuli. The linkage between bilirubin and the serum albumins is very firm and can only be loosened by means of the active cellular work of the liver cells and the cells of the tubuli of the kidneys. This linkage of the serum bilirubin to the serum albumins — including possibly globin from hemoglobin — is also of great interest for the understanding of the pathogenesis of jaundice. For it is very difficult to understand how bilirubin passes through the capillaries into the tissue spaces and colors the various yellow tissues. I have tried to solve this difficult question by means of a provisional hypothesis in my recent paper "Pathogenesis and different forms of jaundice" (*Acta med Scandinav* 128 25-41, 1947).

TORBEN K. WITH, M D

Rigshospitalet  
Copenhagen

Dr With's letter was referred to Dr Lawrence E. Young, whose reply is as follows

*To the Editor* Although it is now recognized that some substances are excreted by the kidney only as a result of work by the tubular cells, the term "renal filter" is still rather liberally applied in references to the kidney in current medical literature. Boyd, for example, in discussing "indirect" bilirubin in his *Textbook of Pathology* (fourth edition, P 542) states "This type of bilirubin cannot pass the kidney filter." On Page 541 of the same text the following statement is found "If the altered bilirubin is then reabsorbed into the blood, as in obstructive jaundice, it is able to pass the barrier of the renal filter and appears in the urine." Numerous references of this sort could be cited, and in addition the term "renal barrier," which has similar connotations, is currently employed by many writers. Hanger, for instance, states in Cecil's *Textbook of Medicine* (seventh edition, P 856) that "the delayed indirect fraction is retained by the renal barrier."

I agree with Dr With that, in the light of present knowledge, more specific terms might well be used in describing various types of renal activity. It should be made clear, however, that in my review on jaundice I was merely following current usage of the term "renal filter" and was not expressing a personal opinion that bilirubin is excreted by glomerular filtration.

Dr With's informative and thought-provoking paper, "Pathogenesis and Different Forms of Jaundice," raises a number of questions that can be answered only by further experimental and clinical observations. In particular, the manner and extent of the binding of bilirubin by protein and the mechanism by which bilirubin leaves the circulation are not yet clear. The active separation and excretion of pro-

tein-bound bilirubin by renal tubular cells, if it occurs, is without precedent according to modern concepts of renal physiology.

Anyone interested in jaundice will profit from consideration of the material presented in Dr With's recent review.

LAWRENCE E. YOUNG, M D

Strong Memorial Hospital  
Rochester, New York

## RESTORATION OF LICENSE

*To the Editor* At a meeting of the Board of Registration in Medicine held February 19, it was voted to restore the registration to practice medicine to Dr Nathan Gaber, 129 Mt Vernon Street, Boston, as of February 21, 1948.

H QUIMBY GALLUPE, M D, Secretary

State House  
Boston

## "NEGATIVE BRONCHOSCOPY"

*To the Editor* As an ardent follower for over ten years of the Case Records of the Massachusetts General Hospital, I cannot help taking this occasion to raise a question concerning certain statements appearing under Case 34022 in the issue of January 8. This was a case of bronchogenic carcinoma occurring in a lower-lobe bronchus. There was peripheral suppuration and contraction of one of the basal segments, a situation commonly referred to loosely as "atelectasis." There was nothing particularly remarkable about the case as a whole. Bronchoscopy had revealed an inflamed, edematous mucosa with marked obstruction and some purulent secretion. The lobectomy specimen revealed carcinoma and rather extensive bronchiectasis. The surprising thing was the comment by Dr Donald King, seconded by Dr Benedict, that he could not recall such a case with "a negative bronchoscopy." I think anyone who has done much chest work will agree that such a situation is not only not rare but also relatively common among a large group of bronchogenic carcinomas, and that many of them cannot be positively diagnosed by the most expert bronchoscopists prior to exploratory thoracotomy. Furthermore, the bronchoscopy was not actually "negative," except in the sense that it did not clearly reveal tumor. It seems probable that the statement conveyed a different impression than was actually intended. In any event it was most certainly inaccurate.

F J LOVELOCK, M D

Chest Service  
Bellevue Hospital, New York City

Dr Lovelock's letter was referred to Dr Donald S. King, whose reply is as follows

*To the Editor* Thank you for referring Dr Lovelock's letter to me. He has just cause for alarm. The statement as published "I cannot remember any case with cancer in a bronchus with a negative bronchoscopy" is of course not true. I cannot be sure what I said. What I meant to say was "I cannot remember any case with cancer in one of the segmental bronchi to the basal segment of a lower lobe in which we were unable to make a correct diagnosis by means of bronchoscopy." I have not been able recently to review our series of some hundreds of cases of primary bronchogenic carcinoma, but so far as my memory goes the statement as corrected above must still stand. These segmental bronchi are usually easily visualized at bronchoscopic examination. I did not make it clear that I was distinguishing between cancer in the basal segment in the lower lobe and that occurring in the dorsal segment of the lower lobe, the middle lobe or the upper lobe. Bronchoscopic visualization is much more difficult in these areas.

DONALD S. KING, M D

1101 Beacon Street  
Brookline, Massachusetts

## HEALTH MENACE IN CROWDED TRANSPORTATION FACILITIES

*To the Editor* It is to be hoped that the members of the Massachusetts Legislature will realize that the problem of meeting the transportation needs of southeastern Massachusetts as a result of the announced discontinuance of train service on the Old Colony Railroad has its medical as well

as its economic aspects. If the Metropolitan Transit Authority takes over this responsibility and continues its policy of furnishing 60 or even as many as 80 seats for every 100 passengers, it will mean crowded cars and many passengers standing. Crowded cars afford an opportunity for the easy and rapid spread of respiratory infections during a period when an epidemic is prevailing. The tired worker or businessman, who must stand all or much of his way home is quite susceptible to infection; his disposition is not improved by a trying trip from work, and he does not contribute to a happy home. It makes one shudder to think that many more thousands may be added to the crush and pushing in already overcrowded trains and subway stations.

Sound public health policy demands a seat for every commuter. It demands protection of the older and handicapped person in the rush for the car door and seats. It is evident that adequate and comfortable transportation facilities will reap a benefit in the health and efficiency of the public that will compensate for possible deficits in operation of transportation facilities.

HAROLD L. HIGGINS, MD

322 Franklin Street  
Newton

## BOOK REVIEWS

*Deal by the Tail*. By Langston Moffett. 8° cloth, 431 pp. Philadelphia: J. B. Lippincott Company, 1947. \$3.00.

This novel tells the story of a man afflicted with a perpetual desire for alcohol. He traveled the world over and finally after fifteen years of drunkenness conquered his desire by self-renunciation and with the help of love. This powerful story is well written and the plot well sustained to the end. It should be in all special collections on alcohol.

*Medicine in the Changing Order*. Report of the New York Academy of Medicine Committee on Medicine and the Changing Order. 8°, cloth 240 pp. New York: The Commonwealth Fund, 1947. \$2.00.

The Committee on Medicine and the Changing Order was organized in 1943 with a membership of thirty-three physicians and seventeen representatives of allied professions and lay persons. The physicians were chosen because of their interest in medical education and public health. The lay members were selected from the fields of ministry, law, social welfare, hospitals, insurance, labor and industry. The objectives of the research were defined as follows: "To be informed on the nature, quality, and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future, to define in particular how these changes are likely to affect medicine in its various aspects, to determine how the best elements in the science of medicine and in its services to the public may be preserved and embodied in whatever new social order may ultimately develop." After a preliminary study and investigation lasting sixteen months, eleven subcommittees were formed to study, especially medical education and graduate and postgraduate medical education, internship, the hospital administration of public health services, extension of medical services, the cost of diagnostic and consultant services, industrial medicine, rural medicine, nursing and dentistry. The committee also selected the titles and authors of twelve monographs to be published by the Commonwealth Fund. These monographs have been noted or reviewed from time to time in these columns.

This general report summarizes the work of the committee in the various fields mentioned above. The report opens with a chapter on the origins of present problems in American medicine and concludes with one on "the method and goal." The committee does not approve compulsory health insurance at present and disapproves any form of prepaid full coverage insurance to be applied as suitable for all sections of the country.

In an over-all program the following principles are emphasized: In extending medical service and perfecting its organization, quality must be preserved; provision of public health services is a primary essential; improvement in medical service requires effective use of hospitals with adequate facilities; success will require trained professional and nonprofessional

personnel; for optimal results, organization and co-operation of physicians are required in the improvement of medical services; voluntary prepayment plans are needed; the goal should be comprehensive medical service; extensive education for both physicians and the public will be required; progress in the extension of medical service must be varied and adapted to the needs of the community; and finally Government aid will be required. Each of these points is discussed at length. The report and collateral volumes are well published in a uniform series. The New York Academy of Medicine and the Commonwealth Fund are commended for completion of this valuable study and its publication in an inexpensive form: no volume costing more than \$2.50, the average price being \$1.61 a volume and the price of the complete set being \$20.25. The series is highly recommended for all libraries, medical and general.

*Rhinoplasty and Restoration of Facial Contour. With special reference to trauma*. By Jacques W. Mallinac, MD. 8°, cloth, 327 pp. with 214 illustrations. Philadelphia: F. A. Davis Company, 1947. \$7.50.

As the title of this book indicates, the author has made an attempt to cover the entire field of traumatic surgery of the nose, from the repair of simple septal deviations to the complex reconstruction of nasal loss.

The book essentially a monograph describing the author's approach to the various types of nasal deformities of traumatic origin is divided into thirteen chapters covering 312 pages. The general arrangement of the chapters is good. The volume is well illustrated with photographs and explanatory diagrams. The classification of deformities is somewhat confusing. The diagrams and their legends are not always clear but on the whole are good.

The author justly condemns the use of complicated appliances in the correction of nasal deformities and fractures. However, the reviewer finds that the author contradicts this point when he describes a rather complicated and wholly unnecessary method for the immobilization of comminuted nasal fractures on Pages 94 to 97.

Chapters VI and VII are particularly good. In the former the various types of skin grafts, flaps and supporting structures used in rhinoplasty reconstruction and the relative merits of each are described; the discussion of the place for transplantation of cartilage and bone as well as the sequelae when used improperly is well taken. The latter chapter, which describes the severe types of septal malformations and their correction, should prove useful to many rhinologists.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Laboratory Manual of Microbiology for Nurses*. By Elizabeth S. Gill, S.B., instructor in nursing, Department of Nursing College of Physicians and Surgeons, Columbia University; and James T. Culbertson, Ph.D., professor of bacteriology and parasitology, University of Arkansas School of Medicine. 4° paper, 116 pp., illustrated. New York: G. P. Putnam's Sons, 1947. \$1.50.

The authors of this manual believe that nurses should be taught the proper methods of handling pathogenic bacteria and the working exercises in the manual are designed to serve as guides in such instruction under proper supervision. Beginning with work on nonpathogenic micro-organisms for the purpose of teaching the student proper techniques and procedures and the use and care of the microscope, the student is carried forward to the study of the important families of bacteria, the spirochetes, yeasts and molds, protozoans, helminths and arthropods. Two appendices list reagents and solutions, and sources of supply for materials. A list of books for reference concludes the volume. The material is well and conveniently arranged and the manual should prove a valuable for its indicated purpose.



memberships are open to any person interested in blood banking

Requests for applications for membership or general information should be addressed to Miss Marjorie Saunders, LL B, Secretary, American Association of Blood Banks, 3301 Junius Street, Dallas, Texas

#### AMERICAN PUBLIC HEALTH ASSOCIATION

The seventy-sixth annual meeting of the American Public Health Association will be held in Boston from November 8 to 12 inclusive. Representatives from all parts of the United States, from Canada, Cuba and Mexico and from Latin American countries, as well as delegates from Europe and Asia, will attend. The following related organizations will hold their annual meetings at the same time and in the same place as the Association: American School Health Association, Association of Maternal and Child Health and Crippled Children's Directors, Association of Reserve Officers of the United States Public Health Service, Association of State and Territorial Health Officers, Conference of Municipal Public Health Engineers, Conference of Professors of Preventive Medicine, Conference of State and Provincial Public Health Laboratory Directors, Conference of State Directors of Health Education, Council of State Directors of Public Health Nursing, National Committee of Health Council Executives, and Public Health Cancer Association.

An extensive scientific program is in preparation, with particular attention to problems of public-health dentists, engineers, epidemiologists, food and nutrition specialists, health officers, industrial hygienists, laboratory workers, maternal and child health experts, public-health educators, public-health nurses, school health specialists and vital statisticians.

#### RESIDENCY IN PSYCHIATRY AT JOSEPH H PRATT DIAGNOSTIC HOSPITAL

A new residency in psychiatry for one-year service is immediately available at the Joseph H Pratt Diagnostic Hospital, Boston.

Service will consist largely of diagnosis and management of patients with neuroses and with personal and emotional complications of disease. Applicants should have an internship as a minimum of training.

In general residencies will begin on January 1 or July 1, except for the residency mentioned above.

Applications should be addressed to Mr Richard T Viguers, administrator.

#### MEDICAL ASSOCIATION OF THE STATE OF ALABAMA

The annual meeting of the Medical Association of the State of Alabama will be held in Mobile from April 15-17 (secretary, D L Cannon, M D, 519 Dexter Avenue, Montgomery 4, Alabama).

#### ARKANSAS MEDICAL SOCIETY

The annual meeting of the Arkansas Medical Society will be held in Little Rock from April 15-17 (secretary, W R Brooksher, M D, 602 Garrison Avenue, Ft Smith, Arkansas).

#### CALIFORNIA MEDICAL ASSOCIATION

The annual meeting of the California Medical Association will be held in San Francisco from April 11-14 (secretary, L H Garland, M D, 450 Sutter Street, San Francisco 8, California).

#### FLORIDA MEDICAL ASSOCIATION

The annual meeting of the Florida Medical Association will be held in St Augustine from April 12-14 (secretary, Robert B McIver, M D, Box 1018, Jacksonville 1, Florida).

#### LOUISIANA STATE MEDICAL SOCIETY

The annual meeting of the Louisiana State Medical Society will be held in Monroe from April 12 to 14 (secretary, P T Talbot, M D, 1430 Tulane Avenue, New Orleans 13, Louisiana).

#### TENNESSEE STATE MEDICAL ASSOCIATION

The annual meeting of the Tennessee State Medical Association will be held in Nashville on April 13 and 14 (secretary, W M Hardy, M D, 706 Church Street, Nashville 3, Tennessee).

#### SOCIETY MEETINGS AND CONFERENCES

##### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 25

###### FRIDAY, MARCH 26

\*9:00-10:00 a.m. The Distribution of Amino Acids between Cells and Extracellular Fluid Dr Halvor Christensen Joseph H. Pratt Diagnostic Hospital

\*10:00 a.m.-12:00 m. Medical Staff Rounds Peter Bent Brigham Hospital

###### MONDAY, MARCH 29

\*12:15-1:15 p.m. Clinicopathological Conference Peter Bent Brigham Hospital

8:15 p.m. New England Heart Association Beth Israel Hospital, Boston

###### TUESDAY, MARCH 30

\*12:15-1:15 p.m. Clinicoroentgenological Conference Peter Bent Brigham Hospital

\*1:30-2:30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital

###### WEDNESDAY MARCH 31

\*9:00-10:00 a.m. Radioactive Phosphorus Therapy Dr Bruce Brown Joseph H Pratt Diagnostic Hospital

\*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater, Children's Hospital

\*Open to the medical profession

MARCH 22-24 and 26 Edward K. Dunham Lectures Page 419

MARCH 23 Norfolk District Medical Society Page 384 issue of March 11

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons American Industrial Hygiene Association American Conference of Governmental Industrial Hygienists American Association of Industrial Nurses Inc and American Association of Industrial Dentists Hotel Statler, Boston

MARCH 29 New England Heart Association Page 419

MARCH 30-APRIL 1 American Association of Industrial Physicians and Surgeons Page 419

APRIL 7-9 American Laryngological, Rhinological and Otolaryngological Society Page 419

APRIL 7, 9, 14 and 16 American Trudeau Society Page 240 issue of February 12

APRIL 8 Endometriosis Dr John Fallon Pentucket Association of Physicians 8:30 p.m. Haverhill

APRIL 10 American Congress of Physical Medicine Page 344, issue of March 4

APRIL 12 Harvard School of Public Health Page 384, issue of March 11

APRIL 13 Harvard Medical Society Amphitheater, Building D, Harvard Medical School

APRIL 19-23 American College of Physicians Page xiii issue of July 31

APRIL 29-MAY 2 American Academy of Pediatrics Page 240 issue of February 12

MAY 6 Suffolk Censors' Meeting Page 344, issue of March 4

MAY 6-8 American Association for the Study of Goiter Page xiii issue of July 31

MAY 16-22 American Board of Obstetrics and Gynecology Inc Page 344, issue of March 4

MAY 16-23 International College of Surgeons Page 136, issue of January 22

MAY 17-20 American Urological Association Hotel Statler Boston.

MAY 18-22 American Association on Mental Deficiency Copley Plaza Hotel, Boston

MAY 20-25 American Board of Ophthalmology Page 170 issue of January 29

MAY 25-27 Massachusetts Medical Society Annual Meeting Hotel Statler, Boston

JUNE 21 and 22 American Society for the Study of Sterility Page 384 issue of March 11

JUNE 28-30 American Academy of Pediatrics Hotel Schroeder, Milwaukee Wisconsin

(Notices concluded on page xia)

# NOTICES (Concluded from page 420)

- July 12-17 First International Polio-myelitis Conference Page 36  
 Issue of January 7  
 August 11-21 International Congress on Mental Health. Page 344  
 Issue of March 4  
 August 23-26. International Society of Hematology Page 419  
 August 26-28. American Association of Blood Banks. Page 420  
 September 13-15 American Academy of Pediatrics. Olympic Hotel  
 Seattle Washington  
 September 20-23 American Hospital Association Page 310 issue of  
 February 26.  
 September 29 Mississippi Valley Medical Editors Association  
 Page 170 issue of January 29  
 October 6-9 American Board of Ophthalmology Page 10 issue of  
 January 29  
 November 8-12. American Public Health Association Page 420  
 November 20-23. American Academy of Pediatrics. Annual Meeting  
 Chalfont Haddon Hall Hotel, Atlantic City New Jersey

## DISTRICT MEDICAL SOCIETIES

### FRANKLIN

May 11 Annual Meeting Hotel Weldon Greenfield

### MIDDLESEX EAST

March 24  
 May 17 Annual Meeting  
 Meetings will be held at the Bear Hill Golf Club Wakefield

### NORFOLK

March 23 Harvard Night

### PLYMOUTH

April 15 State Farm Bridgewater  
 May 20 Lakewood Sanatorium, Lakewood

### SUFFOLK

May 6. Censors Meeting

### WORCESTER

April 14 Worcester Hahnemann Hospital  
 May 12. Annual Meeting

## Washingtonian Hospital

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## TUFTS COLLEGE MEDICAL SCHOOL

### Postgraduate Division

### Courses for the General Practitioner

**INTERNAL MEDICINE**, commencing April 6 for one or three months  
 Didactic lectures, conferences, and demonstrations of clinical applica-  
 tions. Special emphasis on proved diagnostic and therapeutic  
 methods. Dr. Robert P. McCombs in charge. Tuition fees one month  
 \$100 three months \$250

**CARDIOLOGY**, April 6-8. Practical applications of diagnosis and  
 therapy emphasized. Dr. Hiram Magendanz in charge. Tuition fee \$40

**OPHTHALMOLOGY**, April 6-30. The treatment of the commoner  
 external eye diseases taught through demonstration. Instruction in  
 the proper use of the ophthalmoscope with interpretations of the  
 normal fundus and fundus lesions in relation to general medicine. Dr.  
 Joseph I. Sperber will conduct the course at the Boston City Hospital.  
 Tuition fee \$75. Ophthalmoscope required

**DERMATOLOGY**, April 12-16. Diagnosis and treatment of com-  
 mon skin diseases, occupational dermatoses reviewed according to  
 toxicology, practical management, and medical aspects. Dr. John G.  
 Downing in charge. Tuition fee \$40

**RADIOLOGY**, May 13-14. A three-day full time course in chest-ray  
 Normal anatomy, physiology and pathology will be demonstrated  
 including roentgenologic interpretations of the heart and lungs in health  
 and disease. Dr. Alice Ettinger in charge. Tuition fee \$25

All courses may be taken under the G.I. Bill of Rights  
 upon presentation of a VA Certificate of Eligibility

For application forms and further information address

Director Postgraduate Teaching  
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## THE TREATMENT OF ARTERIAL EMBOLISM\*

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BOSTON

ALTHOUGH doctors since the time of William Harvey may have had some conception of the pathologic physiology of thrombosis and embolism and although John Hunter,<sup>1</sup> in 1794, reported intravascular coagulation occurring during life it was not until the time of Virchow<sup>2</sup> (1845) that arterial embolism was clearly described and until later in the century (1895) that the operation of embolectomy was first attempted by Ssabanejeff<sup>3</sup> in Russia. From then until 1911 embolectomy was performed a dozen or more times without success before Labey<sup>4</sup> first successfully removed an embolus from the femoral artery. A short time later Key,<sup>5</sup> in Sweden, was also successful. During the next ten years, Key demonstrated the possibilities of the operation and expanded its use to the utmost in the medical system of Sweden. In ten years Swedish authors were able to report results in 382 cases of embolectomy for arterial embolism of the extremities.<sup>7</sup> At that time numerous small series were first reported from clinics in this country,<sup>8-14</sup> so that by the year 1932 the medical profession had been able to form some preliminary conclusions regarding the place of surgery in this condition.

These conclusions were that arterial emboli usually occur in patients with heart disease who are in middle age, that the most common site of lodgment is a bifurcation of a major artery, usually the bifurcation of the femoral vessels, and that removal of the embolus before ten hours from onset have elapsed often, but not always, saves the limb. Simultaneously with the acceptance of these general conclusions a step forward was taken in the conservative treatment of acute arterial occlusion. Intermittent positive and negative pressure was introduced by Herrmann and Reid,<sup>15</sup> and intermittent venous occlusion by Collens and Wilensky.<sup>16</sup> The oscillating bed has been a more modern improvement on this principle. The role of arterial and arteriolar spasm in acute occlusion and the possibility of relief by interruption

of the sympathetic pathways, either surgically or otherwise, were becoming familiar in 1934.<sup>17, 18</sup> It was at the same time that the purification of heparin by Charles and Scott<sup>19</sup> to the point where it could be used therapeutically furnished a logical means of preventing the blockage of vital collateral circulation by the distal propagating thrombus that follows embolism.<sup>20, 21</sup> With these new weapons available a few authors have suggested that surgery in the treatment of arterial embolism should be, if not abandoned, at least relegated to a position secondary to the newer conservative methods.<sup>18, 22, 23</sup>

It was with these considerations in mind that we undertook to examine our own experience with arterial emboli to determine what place, if any, the operation of embolectomy should play in the therapy of this condition. We have carefully studied the records of 98 patients who suffered 172 arterial emboli during the period 1937 to 1946.

When we first examined the record we discovered that although the operation is well known and the condition is presumably common, embolectomy was performed only forty-three times in twenty-two years.<sup>24, 25</sup> This is a frequency of two operations per year in a hospital to which an average of 6842 patients are admitted and in which an average of 4637 operations are performed each year. That this infrequency is not confined to our hospital, however, is testified to by the small size of most individual series reported and by the fact that McClure and Harkins<sup>26</sup> found only 690 cases reported in the world literature in thirty-three years.

For a better consideration of the disease as a whole, the first section of this paper is devoted to statistical matters concerning all emboli wherever lodged, the second section being confined to the limb emboli for which more specific means of therapy are available.

### GENERAL CONSIDERATIONS

#### *Sites of Embolism*

Figure 1 shows the sites of lodgment of the 172 emboli in the series. Of the total group 110 cases, or 63.9 per cent, occurred in the limbs. Table 1

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presents a comparison of the sites of peripheral emboli with other figures from the literature

There is a constant statistical trend of incidence at the various sites regardless of the source of the figures. It must be emphasized that the data presented in Figure 1, which shows the frequency of the diagnosis of emboli to the brain, spleen, kidney and skin, were obtained from clinical statistics as listed in a diagnosis file. In view of the fact that these

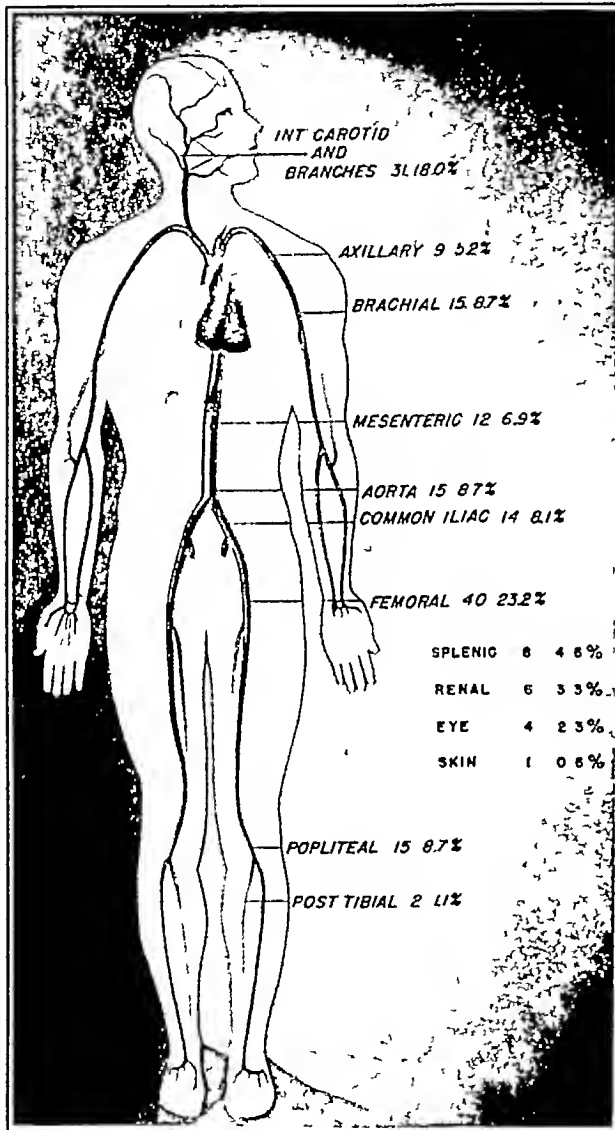


FIGURE 1 Sites of Lodgment of 172 Arterial Emboli

diagnoses are often the least important of a group of major primary ones in a given case, it is probable that they are frequently not mentioned in the final list. It is certain, therefore, that the incidence of these particular emboli as listed is lower than the actual incidence. An examination of the diagnoses in the autopsy file during the same period shows an incidence of emboli to brain, spleen and kidney considerably higher than that derived from the

clinical study (Table 2). Like the clinical statistics, however, these figures cannot be considered representative of the whole picture, because they obviously do not include surgical and nonlethal emboli. In Bull's<sup>26</sup> material also the incidence of emboli to internal organs (such as the spleen and kidneys) at autopsy was higher than that in clinical figures.

The possible sources of arterial emboli have been listed by Agar<sup>26</sup> as pulmonary veins, mural thrombi in the heart, mitral-valve vegetations, atheromatous plaques in the aorta and, very rarely, the systemic veins or the right side of the heart through a patent interventricular septum or foramen ovale as originally described by Cohnheim.<sup>27</sup> To these Gross,<sup>28</sup> in a report on the occurrence of arterial emboli in children, has added thrombus from a closing ductus arteriosus. The embolus usually consists of a thrombus that has broken away from one of the sites described above. The possibility that emboli made up of fragments of tumor invade the large arteries or, more logically, the pulmonary veins, become detached and lodge in the periphery has long been postulated. That this actually occurs is shown in the interesting case reported by Groth<sup>29</sup> in which a sarcoma of the right hip traveled to the lung as a venous embolism and from there at a later date became an embolism to the left femoral artery. From here it and its very long propagating thrombus were removed surgically, and the leg was saved. Pathological examination of the amputated right leg, a specimen of tissue from the lung and the embolotomy specimen from the left femoral artery showed identical tumors. Emboli consisting of retained metallic projectiles have also been reported.<sup>30</sup>

The most common source of emboli is generally considered to be intracardiac. Danzis<sup>9</sup> states that 60 per cent are due to cardiac disease. Koucky et al.<sup>11</sup> state that 13 of their 25 patients had auricular fibrillation. Generally, the elucidation of etiologic factors has not been clear from the data presented. This has not been true in our study (Table 3), which shows that in 87 of the 98 patients, or 88.7 per cent, a clinical diagnosis could be made that gave presumptive evidence of a source of embolism within the heart (Fig 2). It is our impression from these observations that the presence or absence of a coronary occlusion, auricular fibrillation or bacterial endocarditis should offer a powerful argument for or against the diagnosis of arterial embolism, particularly since of the 11 patients with embolism from "undetermined" cause the records of 9 are not adequate to exclude any one or all of these etiologic factors. In only 2 patients did all the causes seem to be entirely excluded.

Since auricular fibrillation with presumably auricular thrombosis was the major cause of embolism it is of some interest to examine the causes of the fibrillation in these 64 cases (Table 4). It can be seen that rheumatic heart disease was responsible for about

two thirds of the cases of fibrillation and arteriosclerotic heart disease for the remainder. Although fibrillation due to thyrotoxicosis has been reported as causing emboli,<sup>22</sup> no such cases occurred in this series.

It has often been taught that drugs that restore a fibrillating auricle to normal rhythm may precipitate emboli. It is of interest that this sequence

patients with mural thrombi due to myocardial infarction was fifty-seven and two-thirds years, which is, as might be expected, slightly above the average. The average age of the 7 patients whose emboli were caused by bacterial endocarditis was forty-five and a half years, or slightly below the average. The average age of the 64 patients who suffered from emboli originating in auricular thrombi on the basis

TABLE 1 Sites of Peripheral Emboli including Aortic Bifurcation

SITE	MASSACHUSETTS GENERAL HOSPITAL CASES	CASES REPORTED BY KAY <sup>14</sup>	CASES REPORTED BY PETITPIERRE <sup>21</sup>	CASES REPORTED BY DANIEL <sup>2</sup>
Subclavian artery	0	0	1 (0.7%)	2 (1.5%)
Axillary artery	9 (8.2%)	45 (11.8%)	10 (7.7%)	7 (5.4%)
Brachial artery	15 (13.6%)	1 (0.3%)	10 (7.7%)	19 (14.7%)
Radial and ulnar arteries	0	2 (1.4%)	2 (1.4%)	1 (0.7%)
Aorta	15 (13.6%)	17 (4.5%)	12 (9.3%)	11 (8.5%)
Iliac artery	14 (12.7%)	65 (1.2%)	26 (20.1%)	23 (17.8%)
Femoral artery	40 (36.4%)	208 (54.4%)	57 (44.5%)	52 (40.3%)
Popliteal artery	15 (13.6%)	41 (11.2%)	10 (7.7%)	12 (9.2%)
Posterior tibial artery	2 (1.8%)	0 (0.5%)	1 (0.7%)	2 (1.5%)
Totals	110	38	129	129

of events could not be established in any of our patients.

### Sex and Age

The sex and age were determined in 97 of the 98 patients. There were 46 female and 51 male patients. The average age was fifty-two years, with extremes of twelve and seventy-seven years. The ages by decades are demonstrated in Figure 3. The youngest patient suffered a cerebral embolism from a subacute bacterial endocarditis superimposed on a congenital deformity described as the tetralogy of Fallot. The next youngest patient was twenty years of age, the embolism being caused by an auricu-

lar fibrillation was fifty-two years, or exactly at the over-all average. This group contained both the oldest and the next to the youngest patients. Table 4, which shows the basic heart disease in the patients with auricular fibrillation and demonstrates that only about two thirds of them suffered from rheumatic heart disease (most of the remainder having arteriosclerotic heart disease), explains the broad range of age in these patients.

The statistics from this study are similar to those reported by Petitpierre<sup>21</sup> in his group of 129 cases of embolism. He found the peak incidence in the fifth and sixth decades. There was a slight preponderance of female over male patients (a ratio of 63:51).

### Differential Diagnosis

In unoperated and unautopsied patients the diagnosis of embolism is always presumptive. It is for

TABLE 2 Sites of Embolism in 74 Cases in 11 000 Autopsies

SITE	NO. OF CASES
Cerebral artery	54
Central retinal artery	3
Internal carotid artery	1
Vertebral artery	1
Coronary artery	8
Pancreatic artery	1
Mezenteric artery	12
Renal artery	7
Splenic artery	4
Brachial artery	1
Aorta	5
Iliac artery	3
Femoral artery	5
Popliteal artery	3
Legs	2
Fingers and toes	1
Total	91

lar thrombus due to auricular fibrillation. The basic disease was rheumatic heart disease with mitral stenosis. It is of some interest to consider the average age of the groups when they are divided according to etiology. The average age of the 15

TABLE 3 Causes of Arterial Embolism in 94 Patients

CAUSE	NO. OF CASES
Auricular fibrillation	64
Myocardial infarction	15
Subacute bacterial endocarditis	7
Auricular fibrillation and myocardial infarction	1
Undetermined	11
Total	98

this reason that most series that have been published deal solely with operative cases. Conditions that may be confused with emboli are chiefly two in number: arterial thrombosis and acute thrombophlebitis of the deep veins of an extremity. The former is much more frequent than the latter. In

acute arterial occlusion in a patient with arteriosclerosis, thrombosis, as pointed out by Linton,<sup>11</sup> can never be ruled out until direct observation of the vessel is made. In spite of the fact that the lodgment of an embolus is a severe vascular accident and according to most descriptions is accompanied

this differential diagnosis in difficult cases must not be persisted in too long. In doubtful cases it is better to err on the side of embolism, since therapy cannot wait upon academic proof.

The other condition that in rare but significant cases must be differentiated from embolism and from



FIGURE 2 Auricular Thrombosis

Photograph of the heart obtained at autopsy in a fifty-four-year-old man who, having had auricular fibrillation for eleven years due to rheumatic heart disease, entered the hospital in heart failure, from which he died eleven days later. Two episodes of arterial embolism occurred before death, one to the right popliteal artery one month before admission, and the other to the abdominal aorta two days before death.

by a sudden onset of severe pain, only 69 per cent of our patients experienced a sudden onset of emboli and only 55.8 per cent suffering from limb emboli had severe pain.

The site of the vascular occlusion is of some help in the differential diagnosis of the thrombosis.

TABLE 4 Causes of Auricular Fibrillation in 64 Patients Suffering Arterial Emboli from Auricular Thrombi

CAUSE	NO. OF CASES
Rheumatic heart disease	41
Arteriosclerotic and hypertensive heart disease	17
Pick's disease (polyserositis)	1
Unknown	5
Total	64

Table 5 shows the location of 149 cases clinically diagnosed as arterial thromboses, excluding those of the coronary vessels, in 147 patients during the same period under study. The higher incidence of popliteal and mesenteric thrombosis in this table is of some significance in differentiating thrombosis from embolism. It has only a statistical value, however, since both popliteal embolism and acute femoral thrombosis occur in a significant number of cases. The clinical demonstration, or lack of it, of a source of embolism must chiefly be relied upon. As pointed out below, however, attempts to make

thrombosis as well as acute thrombophlebitis. As shown by Leriche and Kunlin,<sup>17</sup> Danzis,<sup>9</sup> Edwards,<sup>12</sup> Ochsner and DeBakey<sup>34</sup> and Fontaine and Forster,<sup>35</sup> massive blockage of the deep venous spaces of the leg may throw the arteries into such a degree of spasm that the palpable pulses can disappear. A suggestive line of skin demarcation can ensue and even lead to gangrene. Careful inspection of the

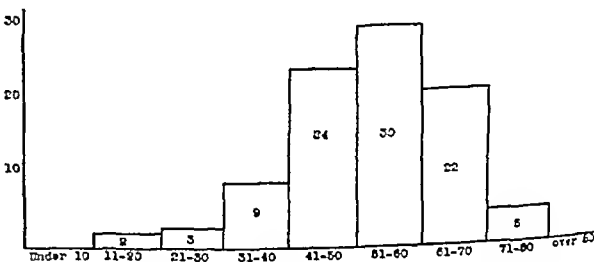


FIGURE 3 Incidence of Arterial Emboli according to Decades

limb for venous engorgement, lack of muscular paralysis and anesthesia and the use of an oscillometer or aneroid sphygmomanometer to detect the presence or absence of oscillation in the calf will make this differential diagnosis.

## EMBOLISM TO LIMB ARTERIES

The object of this section is to discuss the prognosis without treatment of arterial emboli to the major limb arteries, the types of treatment available and the results of these methods in the hands of others and in our own. Table 6 gives a composite view of our results.

## Results with No Treatment

It is generally conceded that arterial emboli to the upper limb that are untreated carry a better prognosis than those to the lower limb.<sup>4, 12</sup> The cor-

TABLE 5 Sites of Acute Arterial Thromboses in 147 Patients (Coronary Thrombosis Excluded)

SITE	NO OF CASES	PER CENTAGE
Cerebral artery	4	2.7
Eye*	2	1.3
Vertebral artery	1	0.6
Mesenteric artery	28	18.9
Subclavian artery	1	0.6
Axillary artery	2	1.3
Brachial artery	4	2.7
Aorta	4	2.7
Iliac artery	2	1.3
Femoral artery	20	13.5
Popliteal artery	41	27.6
Posterior tibial artery	21	14.1
Leg*	13	8.8
Foot*	3	2.0
Total	146	

rect figures are difficult to obtain, particularly from recent studies, since in all cases at present some form

of treatment was necessary other than amputation if the result had been unfavorable or mere treatment of the basic cardiac disease if it had been favorable.

The rate of limbs saved without treatment seems high. One might say that this figure compares favorably with some statistics on operative results. An important consideration is that in the majority of patients who received no treatment the emboli were to the upper extremity, where the prognosis is known to be better than that in the lower limb. In 23 analyzable cases affecting the upper limb 14 received no treatment, in these cases all limbs were saved. In the lower limb among 24 analyzable cases with no treatment limbs were saved in only 7, and were lost in 17. Thus, the 55.2 per cent salvage for all limbs under no treatment is reduced to 29.1 per cent if only the lower limbs are considered.

## Results with Conservative Treatment

Conservative treatment was available during the whole ten-year period. In 1937 and 1938 the principal conservative methods used were papaverine,<sup>22</sup> paravertebral novocain block<sup>17</sup> and the Pavacex boot for the administration of intermittent suction and pressure.<sup>18</sup> After 1939 the Pavacex boot gave place largely to intermittent venous occlusion and the oscillating bed. The use of the other conservative methods was continued.

Our results are drawn from 38 analyzable cases in which 25 limbs, or 65.8 per cent, were saved by these

TABLE 6. Results of Various Forms of Treatment according to Site in 110 Emboli of Peripheral Arteries

SITE	LIMBS WITH TISSUE SAVED			LIMBS WITH TISSUE LOST			LIMBS NOT ANALYZABLE		TOTALS
	OPERATION	CONSERVATIVE TREATMENT	NO TREATMENT	OPERATION	CONSERVATIVE TREATMENT	NO TREATMENT	OPERATION	NO TREATMENT	
Axillary artery	2	2	5	0	0	0	0	0	9
Brachial artery	1	3	9	0	1	0	0	1	15
Aorta	2	3	1	1	0	5	1	3	15
Iliac artery	0	1	2	1	2	3	2	3	14
Femoral artery	13	9	2	1	5	7	0	2	40
Popliteal artery	0	8	0	0	5	2	0	0	15
Tibial artery	0	0	2	0	0	0	0	0	2
Totals*	18	25	21	1	13	17	4	9	110

\*The total number of cases in which no treatment was given was 47, of which 38 were analyzable and in which 21 limbs (55.2 per cent) were saved. The total number of cases in which conservative treatment was given was 38, of which 38 were analyzable and in which 25 limbs (65.8 per cent) were saved. Operation was performed in 25 cases, of which 21 were analyzable and in which 18 limbs (85.7 per cent) were saved.

of treatment is used. In our cases 110 emboli involved the extremities. Thirteen of these are not suitable for evaluation of treatment since the patients died too soon after admission. Of the remaining 97, 38 received no treatment, and only 21 (55.2 per cent) of limbs were saved. To evaluate fairly these figures, it must be stated that the reason these patients received no treatment was that they were admitted to the hospital so late that the fate of the limb had already been decided by the time they were first observed. No treatment, there-

fore, was necessary other than amputation if the result had been unfavorable or mere treatment of the basic cardiac disease if it had been favorable.

An attempt to evaluate individually the various available forms of nonoperative treatment from our records was fruitless. Most often they were used in combination. The reputation of none of the methods is unblemished by the loss of one or more limbs during or after its use. Heparin, for instance,



was used in 9 cases. The limbs were saved in 5 and lost in 4, in some of the former the drug was employed as a last resort, and in some of the latter the limbs might have been saved without it. On theoretical grounds the use of these adjuncts in patients on whom surgery is impossible or who are waiting for surgery or have had unsuccessful surgery seems logical. Paravertebral block relaxes spasm and opens collateral vessels, and heparin should prevent the distal propagating thrombus. Although there is conflicting evidence concerning the value of inter-

hours<sup>39</sup> — the results in patients who have been operated upon within a very few hours of onset are far better than in those having later operations. The value of statistics must be criticized with this factor in mind.

Table 7 shows the results of surgical treatment gleaned from several series in the literature. The favorable results range between 25 and 50 per cent in the larger series and considerably higher in two smaller series, if one does not exclude patients whose limbs were saved but who died in the hos-

TABLE 7 *Results of Surgical Treatment of Embolism*

SOURCE OF DATA	DATE	TOTAL NO OF CASES	ANALYZ- ABLE CASES	TOTAL LIMBS SAVED	UPPER EXTREMITIES		LOWER EXTREMITIES		MOR- TALITY	REMARKS
					NO INVOLVED	PER- CENTAGE SAVED	NO INVOLVED	PER- CENTAGE SAVED		
Petitpierre <sup>41</sup>	1928	129	126	44 4*	24	45 8	105	23 8	50 0	Prognosis for salvage of limb considered good up to 10 hr.
Danzis <sup>9</sup>	1933	129†	103	47 5	—	58 0	—	28 8	55 8	Rate of limb salvage: 1-4 hr, 62%; 4-8 hr, 50%; 8-12 hr, 25%; 12-24 hr, 21%.
Pearse <sup>18</sup>	1933	282	—	30 0	—	43 5	—	27 5	52 0	Rate of limb salvage under 10 hr, 40%; 11-20 hr, 14%; 21-30 hr, 8%.
Strömbeck <sup>40</sup>	1936	327	120	50 0	24	62 5	96	47 7	63 0	—
Key <sup>41</sup>	1936	48	—	54 1	4	100 0	44	50 0	39 5	Prognosis for salvage of limb considered good up to 10 hr, after 24 hr operation regarded as of "no use."
Lund <sup>18</sup>	1937	27	—	57 7	—	85 7	—	47 4	44 4	—
Reynolds and Jirka <sup>42</sup>	1944	16	13	87 5	—	—	—	—	75 0	Under 18 hr all limbs saved
Massachusetts General Hospital	1937-1941	25	21	85 7	3	100 0	18	83 4	28 6	Under 11 hr all limbs but 1 saved

\*Figure not clear since circulation is listed as restored in 5 cases in which gangrene developed.

†Many patients the same as those of Petitpierre, but series not identical.

mittent venous occlusion<sup>36, 37</sup> and passive vascular exercises our clinical impression has been that these are the most valuable adjuncts of all.

The conservative weapon that we have found least useful has been papaverine. Clinical observations have revealed little benefit from this drug other than a certain amount of pain relief. The experimental work of Abramson<sup>38</sup> and others has shown that this drug produces little improvement in the vascular responses in the limbs.

### Results of Surgical Treatment

A review of the literature reveals that the overall results of embolectomy are disappointing if one wishes to set up as a goal the ideal of 100 per cent survival of limbs and patients. There is as yet little that can be done about patients who die of heart failure or cerebral embolism. We should, however, be able to save 100 per cent of limbs. Since the muscles of a limb can survive complete lack of oxygen for only a limited time — perhaps six to ten

hours of primary heart disease. Some authors argue that surgery in patients who are soon to die of their primary disease is not worth while. There is no question, however, that the prevention of gangrene can spare the patient much suffering. In addition, it is not always possible at a given point during the acute stage of the disease to separate the doomed patients from those destined to survive.

The following analysis of our surgical results is given. Twenty-one patients were operated upon for removal of emboli. Twenty-five operations were performed, 4 patients having two operations each, the second operation being done for occurrence of emboli either at a new site or at the old one.

Four of these emboli were in 3 patients who died so soon that the effect of operation on the limbs could not be determined. Of 21 analyzable limbs, 18 or 85.7 per cent, survived.

In the 3 cases in which the limbs were lost there was technical difficulty in removing the embolus in 2 cases because the clot was adherent to the artery.

There was difficulty in the other case because of inability to remove all the clot satisfactorily from an embolus at the aortic bifurcation through bilateral femoral incisions. The elapsed time from onset to embolectomy in the former 2 cases was nine and a half and seventeen hours, and in the latter three hours.

### Mortality and Causes of Death

A total of 38 of the 98 patients died in the hospital, a mortality of 38.7 per cent (Table 8). All patients died of cardiovascular disease. The surgically treated patients showed a mortality of 28.6 per cent, the rate for the nonsurgically treated cases, therefore, being somewhat above the average. The mortality figures from other clinics where the emboli of major peripheral arteries are treated surgically are higher (Petitpierre,<sup>1</sup> 50 per cent, Nyström,<sup>7</sup> 60 per cent, and Strömbeck,<sup>40</sup> 63 per cent).

We consider these results to demonstrate that surgery itself is usually not harmful. Exceptions to this statement may be that operation on the abdominal aorta, since it cannot be done under local anesthesia, is poorly tolerated by the desperately ill patient, that operation on the popliteal artery is technically so difficult to perform without injury to collateral vessels or constriction of the small bifurcation of the artery by the suture line that conservative treatment is regarded as the one of choice, and that in a patient with very advanced peripheral arteriosclerosis the likelihood of thrombosis at the arteriotomy suture line after embolectomy is great, since the next traumatic suturing of an irregularly calcified arterial wall may be impossible—in such a patient, therefore, surgery may be decided against on this basis. The 1 death in this series that could possibly be attributed to surgery occurred on the operating table in collapse of a very sick forty-year-old woman with rheumatic heart disease who had just had an embolus removed from the aorta. Surgery should not be condemned on the basis of such a case, however, since 2 patients in the group died under similar circumstances on the way to the operating room before any anesthesia had been given or incision made.

### Time Factor in the Treatment of Embolism

The speed with which the patient is brought to the surgeon after the embolism has struck is known to be of the utmost importance. Key considered ten hours to be the period chosen as a dividing line between favorable and unfavorable results. Table 7 shows that in the experience of others this figure has remained the best approximation available. Experimental evidence also suggests that it is accurate.<sup>39</sup>

The average elapsed time from onset to surgery in the 16 patients whose limbs survived was eight

and three-quarter hours. The longest elapsed time was eleven hours, except in a case in which a femoral embolism was removed sixty hours after onset, in this patient a pregangrenous state of two toes was converted into a viable foot by the procedure, pulses that had previously been absent actually returning to the foot. Although successful late embolectomy has been reported by Hopkins<sup>38</sup> and others, it is the exception rather than the rule that an embolus that has been lodged for this length of time is not so adherent that it cannot be removed.

TABLE 8 Hospital Mortality and Cause of Death in 98 Patients with Arterial Embolism

CAUSE OF DEATH	SURGICAL CASES	NONSURGICAL CASES	TOTAL
Cerebral embolism	—	14	14
Cardiac failure	5	5	10
Myocardial infarction	—	6	7
Myocardial infarction	—	4	4
Pulmonary embolism	—	1	1
Subacute bacterial endocarditis	—	—	—
Unknown	—	1	1
Totals	6 (28.6%)*	32 (41.5%)+	38 (38.7%)

\*Of 21 cases.

+Of 77 cases.

Surgery should not necessarily be abandoned in peripheral embolism because a temporal "deadline" has been passed. Much, of course, depends on the appearance of the limb. If actual gangrene has set in as may happen within two days, embolectomy is not to be considered. If, however, there is calf paralysis, foot anesthesia and marked vasospasm with a line of demarcation that is suggestive only, embolectomy followed by conservative supportive measures should be performed.

### Late Results

When a patient presents himself with an acute arterial occlusion, efforts are primarily directed at saving the limb. It has been shown<sup>40</sup> that even if the tissues of the limb survive complete arterial occlusion there is a likelihood of future difficulty with proper mechanics of the member if the main arterial trunk is allowed to remain obstructed. Strömbeck<sup>40</sup> has left a very complete report on the follow-up examination of a large number of patients. Of the 327 patients, 61 were discharged from the hospital after successful peripheral-artery embolectomy. Of these 61, three fourths lived for one year, half lived for three years, a third lived for five years, and one eighth lived for ten years. At the time of the report 41 patients had died. The cause of death in 20 of these was heart failure in 12 cases was caused by hemiplegia presumably due to embolism to the brain. Strömbeck also mentions that half the patients seen on follow-up study with

limbs that had been saved had numbness or paresthesias

Some fragmentary data are available on 9 of our 14 patients who underwent embolectomy and survived. Of these, 6 have died, 3 of cerebral embolism, 1 of coronary closure, 1 of heart failure and 1 of carcinoma of the esophagus. Of the 3 patients living, 1 had a cerebral embolism with hemiplegia and the further course is unknown. Two others were living and well three and seven years, respectively, after operation.

There is also some information on 10 of the 44 patients who survived nonsurgical treatment. Five remained or became hemiplegic. One of these was well for seven years before dying of cerebral embolism. Another patient died two days after discharge, and another three years after discharge of coronary occlusion. Three patients were living in fair health two years after discharge.

### DISCUSSION

The treatment of arterial embolism is always undertaken as an emergency. It is a nonelective procedure. Patients cannot be referred at leisure to faraway specialists for this treatment. Every community where human beings suffer from rheumatic fever or arteriosclerosis will observe a regular, though small, incidence of arterial embolism. Any doctor, whatever his specialty, might be the nearest to a patient so stricken and be called upon to provide at least first aid. Immediate hospitalization and initiation of definitive treatment should be urged. This treatment does not have a fair chance unless the time factor is considered as paramount. Nystrom<sup>7</sup> has pointed out the benefits to be derived if the whole medical community participates in the treatment of these patients. From our study we have formed the opinion that operation should be performed in all cases in which local anesthesia can be used, with the sole exception of popliteal emboli. Also, aortic embolectomy, which requires a general anesthetic, is the treatment of choice for embolism of the aorta. Conservative treatment, although its results are good in some cases, is justifiable only when the embolism obviously does not endanger the limb, in the rare aortic embolism in which the patient cannot be brought into the proper condition to withstand a general anesthetic, and in popliteal embolism. It is emphasized that if one is forced to use conservative therapy alone it is essential that it be initiated with as much dispatch and urgency as is advocated for surgical treatment. Even though the embolism is for many patients the last milestone on the downward road of serious cardiac disease, lives are saved by embolectomy. It is difficult to doubt the value of the procedure when one reads case reports such as that contributed by Ravdin and Wood<sup>44</sup> in which a young man was reclaimed by aortic embolectomy for a very useful existence. Danzis<sup>9</sup> has said "While the operative

results are far from ideal, much suffering may be spared and many limbs and even lives be saved by prompt intervention and careful surgical technique."

### SUMMARY

A review of 179 arterial emboli in 98 patients is presented. One hundred and ten involved the limbs.

The salvage of 85.7 per cent of 21 limbs, which could be analyzed after embolectomy, is reported.

In 65.8 per cent of conservatively treated arterial emboli, the limb was preserved.

It is concluded that although available conservative weapons are valuable adjuncts to surgery, surgical embolectomy is the treatment of choice in peripheral-artery embolism.

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## IDIOPATHIC HYPERLIPEMIA\*

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**I**DIOPATHIC hyperlipemia, an apparently benign disorder of neutral fat metabolism of unknown etiology, has been reported six times since Buerger and Grütz<sup>1</sup> first described the syndrome in 1932. Thannhauser<sup>2</sup> reviewed the reported cases to the time of the publication of his monograph in 1940. The essential features of this disorder consist of a grossly milky blood serum due to increase in neutral fat content, together with enlargement of the liver and spleen. Xanthomatous lesions of the skin may also be present. Unexplained abdominal colic has occurred in half the cases. A moderate reduction in blood fats has followed dietary treatment, but normal values have not resulted.

### CASE REPORT

H. L., a 26-year-old married veteran was admitted to the hospital on December 11, 1946, because of a chronic, non-productive cough of 10 years' duration. This had become severer after an attack of bronchitis in the preceding July. He had had no other symptoms of any sort.

In early childhood skin lesions, which had extended a yellow matter, had developed on the legs, and later between the ages of 9 and 10, yellow plaques had appeared on the extremities. In 1944 while in Italy the patient had experienced several brief episodes of cramp-like pain in the middle and upper abdomen, accompanied by nausea and vomiting. During hospitalization for these attacks lipemia and splenomegaly were first discovered. After prolonged study he was discharged from the Army. Since then he had remained free of gastrointestinal complaints.

His mother and three siblings were living and well. His father had died of cancer of the bowel. There was no family history of diabetes mellitus or other metabolic disease.

Physical examination disclosed a well-nourished man who was 5 feet 2.5 inches tall and who weighed 125 pounds. The skin and mucous membranes were normal and there were no xanthomatous lesions. Examination of the heart revealed a

soft systolic murmur in the pulmonary area which disappeared on deep inspiration. The lungs were clear and resonant; the abdomen was soft and no tenderness was elicited. A firm liver edge was palpable 2 cm. below the right costal margin in the midclavicular line. The edge of the spleen was easily palpated 6 cm. below the left costal margin. Rectal examination showed external hemorrhoidal tags. The remainder of the examination was within normal limits.

The temperature, pulse and respirations were normal. The blood pressure was 120/80.

Examination of the blood disclosed a red-cell count of 4,900,000 with a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 4,300 with 57 per cent segmented neutrophils, 4 per cent band forms, 36 per cent lymphocytes and 3 per cent monocytes. The urine had a specific gravity of 1.025 and gave a + in + test for albumin and a + reduction of Benedict's solution. The reaction was acid. No Bence-Jones protein was present. Microscopic examination of the sediment was negative. The serum cholesterol was 295 mg. and subsequently 205 mg. per 100 cc. after the patient had been on a fat free diet for 48 hours. The serum bilirubin was less than 0.1 mg. per 100 cc. The alkaline phosphatase was 3.5 Bodansky units. The cephalin flocculation test was + after 48 hours; the fasting blood sugar was 106 mg. per 100 cc. and the prothrombin time 88 per cent of normal; the total protein was 7 gm. per 100 cc., with 3.9 gm. of albumin and 3.1 gm. of globulin. Hemolysis of the erythrocytes began at 0.46 per cent sodium chloride and was complete at 0.38 per cent. The coagulation time was 6 minutes and the bleeding time was 1 minute. A stool was negative for occult blood. The vital capacity was 3800 cc.

A ray film of the skull, chest, spine, long bones and sinuses were normal. An intravenous pyelogram showed the left kidney to be rotated on its longitudinal axis and displaced slightly toward the midline by the enlarged spleen; the contrast substance was excreted to a normal degree and no abnormalities were noted in the urinary tract.

On symptomatic treatment the cough, presumed to be due to chronic bronchitis, disappeared and the patient was discharged on January 2, 1947, without dietary or other restrictions. On February 17 he returned for a blood lipid determination (Table 1) and immediately thereafter he began to suffer from malaise, anorexia, headache, chills and fever.

Physical examination revealed herpes simplex on the lip; otherwise the findings were unchanged from admission.

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The temperature was 100.2°F, the pulse 96, and the respirations 16.

Examination of the blood showed a red-cell count of 4,100,000, with a hemoglobin of 13.4 gm per 100 cc, and a white-cell count of 2410, with 32 per cent segmented neutrophils, 18 per cent band forms, 38 per cent lymphocytes and 12 per cent monocytes. The urine gave a ++ test for albumin and contained no sugar. The sediment was normal. Blood smears were negative for malaria. Blood cultures were sterile. No cold agglutinins were present in the blood serum. An x-ray film of the chest showed no change.

Four days after entry the patient became icteric, and the liver edge extended 10 cm below the right costal margin. The stools became light colored, and the urine became dark, with a positive test for bile. The urinary urobilinogen was 1.8 Ehrlich units in 2 hours, the serum bilirubin 7.8 mg per 100 cc total, with a positive direct van den Bergh reaction, and the cephalin flocculation ++++. The white-cell count

disease<sup>5</sup> revealed no cause for abdominal pain. The history in the case presented above indicates that the patient had had such a pain in Italy in 1944.

Hepatic and splenic enlargement, varying in degree, has been uniformly observed in all the reported cases of idiopathic hyperlipemia. In Holt's patient the organs enlarged after each attack of abdominal pain at the same time that the blood lipids decreased. In 3 cases a decrease in hepatosplenomegaly occurred with the restriction of fat in the diet.

Whether patients with idiopathic hyperlipemia subsequently develop xanthomatous biliary cirrhosis is not known. None of the reported cases of idio-

TABLE 1 Blood Lipids in a Case of Idiopathic Hyperlipemia \*

DATE	TOTAL FATTY ACIDS	NEUTRAL FAT	TOTAL PHOSPHOLIPIDS	SAPONIFIABLE PHOSPHOLIPIDS	TOTAL CHOLESTEROL	CHOLESTEROL ESTERS
1947	mg/100 cc	mg/100 cc	mg/100 cc	mg/100 cc	mg/100 cc	mg/100 cc
February 17†	3370	3202	328	290	250	100
April 30‡	1840	1612	207	—	204	118
July 7†	3730	3420	273	—	290	165

\*Analyses performed by Dr Siegfried J Thannhauser.

†Normal diet.

‡Low-fat diet.

fell to 2000, with 36 per cent segmented neutrophils and 64 per cent lymphocytes.

The patient was placed on a high-carbohydrate, high-protein, low-fat (30 gm) diet. His appetite rapidly returned, and after 6 weeks of bed rest, the serum van den Bergh, cephalin flocculation and urine urobilinogen had returned to normal. Repeated urinary specimens were bile free, but showed a + to +++ test for albumin and a + to +++ reduction of Benedict's reagent. Glucose (100 gm) was administered by mouth. The fasting blood sugar was 85 mg per 100 cc, and at ½ hour, 1 hour, 2 hours and 3 hours, respectively, 162, 128, 86 and 68 mg per 100 cc. The urine gave —, + (olive) + + + (orange) + + (yellow) and — reductions of Benedict's solution in the fasting, ½-hour, 1-hour, 2-hour and 3-hour specimens, respectively. The serum amylase was 11 units per 100 cc.

The patient was discharged on April 4, with instructions to continue the rigid low-fat diet. After a total of 9 weeks on this regimen, the serum lipids showed a marked decrease (Table 1).

On July 7 he reported that he felt perfectly well, but had not been following his diet rigidly. The serum lipids had returned to the original level (Table 1).

Two siblings of the patient were examined, the blood serum of neither was lipemic.

## DISCUSSION

Skin lesions have been observed in 4 of the 6 previously reported cases of idiopathic hyperlipemia. Three patients had yellowish, discrete papules, chiefly on the extensor surfaces of the extremities and on the buttocks. These lesions are also found on the lips, face, palate, eyelids, ears, fingers, toes and scrotum. One patient had a somewhat different type of lesion beginning as vesicles, which soon ruptured, leaving shallow ulcers that persisted for a number of months.<sup>3,4</sup> The history of the patient reported above suggests that he had had both types of lesions in childhood, although the skin was free of xanthomatous lesions during observation.

Colicky abdominal pain has been reported in 3 cases. Exploratory laparotomy in 1 case<sup>3,4</sup> and autopsy in a patient who died of an intercurrent

pathic hyperlipemia have exhibited jaundice. The jaundice in the case reported above is believed to have been a simple infectious hepatitis. In xanthomatous biliary cirrhosis neutral fat is not elevated to the degree reported in idiopathic hyperlipemia, and there is a disproportionate rise in the total cholesterol.

Chronic pancreatitis may be associated with hyperlipemia as well as diabetes mellitus. In many cases the attacks of abdominal pain associated with pancreatitis do not appear differentiable from the pain noted in idiopathic hyperlipemia. It is possible that chronic pancreatic disease is related etiologically to idiopathic hyperlipemia. However, in the only autopsied case of this disorder a normal pancreas was observed.<sup>6</sup>

The prognosis in this condition appears to be excellent. Treatment with lecithin, choline, thyroxin, insulin, liver extract, anterior pituitary extract and lipocain has not significantly altered the blood fats.<sup>1</sup> A low-fat intake has led to reduced blood fat levels, a subsidence of skin lesions and a decrease in the size of the spleen and liver.

## SUMMARY

A case of idiopathic hyperlipemia with hepatosplenomegaly is reported. The findings in the 6 cases of this disorder previously described are reviewed.

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## STREPTOMYCIN TREATMENT IN ACUTE BRUCELLOSIS\*

## Report of a Case with Review of the Literature

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ALL three strains of *Brucella* are known to be sensitive to small concentrations of streptomycin in vitro.<sup>1</sup> This antibiotic has also been shown to protect chick embryos against infection with *Brucella abortus*<sup>2</sup> and to modify the infection to a considerable degree in guinea pigs.<sup>4</sup> Recent studies, however, throw doubt on the efficacy of streptomycin in experimental brucellosis in guinea pigs.<sup>4</sup> The reports that have appeared on the use

with bacteremia gave evidence of improvement, after three separate courses of streptomycin, the last course following splenectomy. Reimann, Price and Elias<sup>3</sup> give data on 3 cases of brucellosis. Fever in the first 2 cases appeared to respond temporarily to streptomycin administration, the third case showed no response. In these cases, no blood cultures were taken during or after treatment and the length of the follow-up period is not specified.

TABLE I Significant Data in Cases of *Brucella* Treated with Streptomycin

AUTHOR	NO. OF CASES	TOTAL DOSE	DURATION OF TREATMENT	BLOOD LEVEL		RESULT
				gm.	microgram per	
Keefer <sup>4</sup>	25	—	5-16	3 0-4 0	—	Decrease in fever
	5	—	—	3 0	—	Decrease in fever
	10	—	—	2 0	—	No response
	5	—	—	3 0-4 0	—	No response
Nichols and Herrell <sup>4, 7</sup>	8	—	—	—	—	No response
	1	14 6	14	1 0	—	Doubtful
	1	43 0	36	1 0-2 0	—	Ultimate recovery after three courses of treatment followed by splenectomy
	1	7 0	7	1 0	—	Doubtful
Reimann et al. <sup>3</sup>	1	54 0	7	1 0	1-4	Relapse after treatment; ultimate recovery
	1	—	6	3 0	9-13	—
	1	—	1	4 0	—	—
	1	—	5	5 0	27	—
Morgan and Hunt <sup>8</sup>	1	24 0	7	4 0	12 19	Decrease in fever; no relapse.
	1	24 0	8	3 0	12	No response
	1	38 75	5	2 0	—	Temporary arrest of bacteremia; relapse after treatment.
	1	—	3	6 0	—	—
Pulaski and Amspacher <sup>10</sup>	6	8 0-63 0	10-20	1 0-3 0	—	No response
	1	32 0	20	1 2-1 1/2	16	Sulfadiazine given concomitantly; recovery
	1	141 0	47	3 0	16	—
	1	16 0	10	—	6-25	No response; relapse
Howe et al. <sup>11</sup>	1	23 0	6	—	16-47	No response
	1	20 5	6	—	3-23	No response; relapse.
	1	19 0	9	2 2	—	No response
	1	27 0	9	2 0	—	Doubtful
Hall et al. <sup>12, 13</sup>	1	118 0	31	3 0-5 0	—	No response; drug-resistant strains; eventual recovery
	1	23 5	8	3 0	33-50	Improvement
	1	78 0	7	4 0	40-90	Improvement
	1	—	—	—	—	—

of streptomycin in the treatment of brucellosis in human beings have so far been equally inconclusive.

Table I lists the significant data on streptomycin treatment in the cases reported in the literature. Reports in which neither blood levels nor daily dosage of streptomycin are clearly specified are not included.

Of the 45 cases of brucellosis reported by Keefer,<sup>4</sup> 30 showed decrease in fever, and 15 showed no response to streptomycin treatment. The incidence of relapse in these cases is not given. Nichols and Herrell<sup>4, 7</sup> have reported 11 cases of brucellosis, giving details in only 3. Only 1 of the patients

Morgan and Hunt<sup>8</sup> present 1 case in which there was no clear-cut clinical response, despite temporary elimination of organisms from the blood stream. Pulaski and Amspacher,<sup>10</sup> in treating 8 patients with bacteremia due to *Brucella*, noted benefit in only 2 cases in which sulfadiazine was given concomitantly, and recommend this combined type of therapy in the treatment of brucellosis. Howe et al.<sup>11</sup> used streptomycin in 3 cases of acute brucellosis without appreciable change in any, 2 cases had relapses after treatment. Hall, Braude and Spink,<sup>12, 13</sup> in 2 cases of chronic brucellosis with bacteremia, claimed no clear-cut effect from streptomycin. In a third case, with endocarditis, these authors noted that organisms recovered during and after thirty-one days' treatment with streptomycin had developed marked resistance to the drug in vitro.

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In 2 additional cases, in which high blood levels were attained, these authors report improvement as a result of therapy. In 2 cases reported as brucellosis by Goetz<sup>14</sup> and Brier,<sup>15</sup> the diagnosis was inconclusive. A definite impression of the effect of streptomycin in the 6 cases of acute brucellosis reported by Finch<sup>16</sup> cannot be gained from the data presented, although a favorable response to treatment is said to have been obtained.

Because of the equivocal results observed to date, it seems worth while to present 1 more case of

chemotherapy, showed no abnormalities. Blood cultures were taken into liver infusion and tryptic digest broth, and were incubated at 37°C in candle jars (approximately 10 per cent carbon dioxide), none being discarded as negative before the end of 3 weeks. Thioglycollate was added to the cultures taken during the period in which the patient was receiving streptomycin. The increased carbon dioxide tension may also have served to reduce the action in vitro of what little streptomycin was added to the cultures with the patient's blood.<sup>1</sup> *Br. abortus* was recovered from the blood on numerous occasions prior to streptomycin therapy, and the strain was identified by growth on differential dye mediums and estimate of hydrogen sulfide production. During and after treatment, all blood cultures remained sterile. The strain was found to be sensitive, in vitro, to 2.0 microgm.

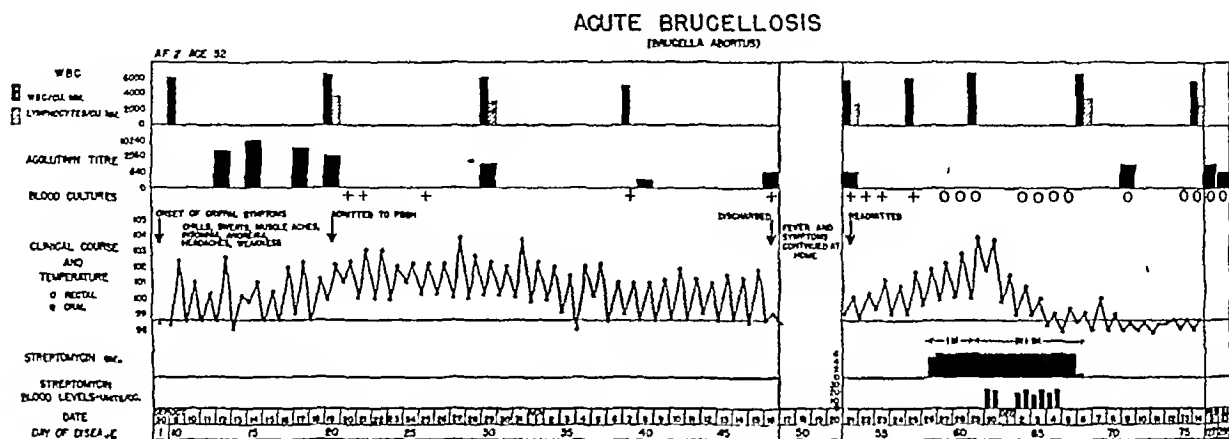


FIGURE 1 Data in Case of Acute Brucellosis

Ten months after the onset of the illness and eight months after completion of treatment, blood cultures were negative, and the agglutination titer was 1:640. The patient remained well up to fifteen months after treatment.

infection due to *Br. abortus*, in which streptomycin was used with some evidence of therapeutic effect.

### CASE REPORT

A 52-year-old man, whose past medical history was not remarkable, was admitted to the hospital on October 19, 1946, 3 weeks after the onset of extreme malaise, anorexia, slight nasal congestion and dry cough. Two weeks before admission, he had had a shaking chill, which was followed by daily afternoon temperature elevations to 100 to 102°F and profuse night sweats. He had consumed unpasteurized milk on numerous occasions prior to the onset of the illness. A blood specimen sent to the Massachusetts Department of Public Health 1 week before admission had shown a titer of agglutinins for *Br. suis* of 1:400, rising 4 days before admission to 1:5000. A presumptive diagnosis of brucellosis had therefore been made by the family physician.\*

Physical examination showed a patient who appeared to be exhausted and was perspiring profusely. The mucous membranes were pale. The liver was palpable three finger-breadths below the right costal margin. The spleen was not felt at any time during the period of the patient's hospitalization. Physical examination was otherwise negative.

The temperature was 101°F by rectum, the pulse 88, and the respirations 20. The blood pressure was 100/70.

Examination of the blood revealed a hemoglobin of 15 gm per 100 cc. and a hematocrit of 45, falling to 39 during the ensuing month. The blood Hinton test was negative. The sedimentation rate varied between 14 and 16 mm per minute (Wintrobe method) as determined on five occasions. The white-cell count was consistently found to be between 5000 and 6000, with 40 to 50 per cent lymphocytes. The urine on admission, as well as on four occasions during

of streptomycin per cubic centimeter of tryptic digest broth. The variations in the titer of agglutinins for *Br. abortus* are shown in Figure 1.

The course of the fever was typical of acute brucellosis. Streptomycin did not become available for use in this case until 5 weeks after admission, and a control period of observation in which no chemotherapeutic or antipyretic agents were administered was thus allowed. Fifty-eight days after the onset of the illness, a course of streptomycin was started.† The patient was given a total of 60 gm, in daily doses of 6 gm (1 gm every 4 hours), over a period of 10 days. He complained of increasingly acute burning, aching and tender swelling at the sites of intramuscular injections, despite the presence of procaine in the injected solutions of streptomycin. By the 4th day of treatment, because of excruciating pain in both gluteal and quadriceps muscle groups, the patient was hardly able to walk, was acutely uncomfortable in any position in bed and was unable to sleep despite sedation. The mode of administration of the drug was therefore altered, so that he received 1 gm intravenously every 4 hours during the day, each dose being dissolved in 400 cc of physiologic saline solution and given over approximately ½ hour, only the midnight and 4-a.m. doses were given intramuscularly as before. This change had no appreciable effect on the established blood levels of streptomycin. Determinations were made shortly before and 1 hour after scheduled intramuscular intravenous doses, to ascertain the minimum and maximum blood concentrations obtained by each route. The blood levels varied between 20 and 25 microgm per cubic centimeter of blood.

During the last 5 days of treatment, the temperature declined rapidly. The patient felt much improved, he suffered no more night sweats, his appetite increased, and the muscle soreness subsided promptly. Audiograms and vestibular-function tests were normal at the conclusion of

\*We are indebted to Dr. F. F. Blumenthal, of Bridgewater, Massachusetts, for referring the patient to this hospital, and for his continued interest and co-operation.

†Streptomycin hydrochloride kindly supplied by Merck and Company, Rahway, New Jersey.

treatment, except for slight high tone deafness. During the first few weeks of convalescence, he complained of definite unsteadiness of gait, occasional dizziness and questionable tinnitus, all of which may have been due to streptomycin toxicity. For approximately 8 months after the completion of therapy the patient continued to improve generally. He returned to work, and had no sign of recurrence of the infection. The vestibular symptoms diminished, but persisted in a minimal degree. On July 27, 1947, 10 months after the onset of illness and 8 months after the beginning of treatment, blood cultures were sterile and the agglutinin titer was 1:640. Fifteen months after treatment the patient was still free of symptoms.

### Discussion

In untreated cases of acute brucellosis, the degree to which recovery takes place is directly related to the efficiency of the individual immune mechanism. In the case presented above, the effect of streptomycin treatment was added to that of the immune response. Both these factors should therefore be considered in any attempt to explain the recovery.

Such an attempt is complicated by the nature of the disease, since, in the light of recent studies by Ruiz-Castaneda<sup>17</sup> confirming earlier observations of Smith,<sup>18</sup> Goodpasture and Anderson<sup>19</sup> and Buddingh and Womack,<sup>20</sup> brucellosis appears to be predominantly an intracellular infection. Meyer<sup>21</sup> has stated more specifically that "selective intracellular parasitism in mesenchyme cells of various organs is of greatest significance in the pathogenesis of Brucella infections." The titer of specific agglutinins by present methods of determination is probably the result of several constantly changing forces: the degree of host parasitization, or the total amount of antigen present, which is affected to a varying extent by the bactericidal power of the blood, the rate of production and total quantity of antibody, and the degree to which antigen and antibody react with each other within the host. A rapidly mounting increment of organisms, multiplying intracellularly and outstripping the production of antibody with which to neutralize circulating antigen, might be evidenced by a declining concentration of agglutinins. Conversely, with the curtailment of bacteremia, either spontaneously or by chemotherapy as in the case reported above, there is presumably some limitation of further host parasitization, and the agglutinin titer might be expected to rise if the immune response continues. A definite fall in agglutinin titer was observed during the first seven weeks of the patient's illness, and shortly after his abrupt clinical recovery, the titer started to rise again. It is possible that chemotherapy at the end of the eighth week of continued bacteremia spared this patient a more protracted course and allowed his own immune mechanism to become effective. However, the fact that resistance to and recovery from infection is not wholly dependent upon the presence of tangible antibody—that is, agglutinins—and must involve other less readily detectable immune factors is attested by the coexistence in the blood of organisms and circulating antibody, not only in brucellosis but also in other infectious

diseases, such as typhoid fever and subacute bacterial endocarditis.

That streptomycin penetrates beyond the cell membrane is suggested by reports on the concentration of the drug in various tissues after its parenteral administration in man<sup>22</sup> and animals.<sup>23</sup> It is thus not illogical to suppose that in the presence of sufficiently high blood concentrations, maintained for adequate periods, streptomycin exerts bacteriostatic or bactericidal action on intracellular organisms. It may be significant that among previously reported cases of brucellosis in which it was possible to decide whether streptomycin treatment had been effective, temporary or lasting benefit was demonstrated only in patients in whom the blood levels reached or exceeded 20 to 30 microgm per cubic centimeter or in whom the daily dose at any time approached 6 gm. It is of interest in this connection that the patient described above received 6 gm a day for ten days, maintaining blood levels between 20 and 25 microgm per cubic centimeter and recovered completely, albeit with minimal signs of streptomycin toxicity. It is probable, however, that the effect of antibiotics on intracellular infections is not all a simple matter of dosage and blood levels, since tularemia, also primarily an intracellular infection, is far more susceptible of cure with streptomycin than brucellosis appears to be.

### SUMMARY

An acute case of brucellosis, in which streptomycin was given in large doses, with apparent success, is presented in detail. In a review of all previously reported cases of brucellosis treated with this antibiotic, it appears that patients in whom the highest blood levels of drug were maintained for even relatively short periods showed more signs of response than those in whom lower blood levels were maintained over relatively longer periods. Therapy at high dosage, however, is not without risk of streptomycin intoxication, as evidenced by the slight though definite vestibular impairment persisting in the case reported.

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## THE VALUE OF A SPECIAL AURICULAR LEAD AND OF CAROTID-SINUS PRESSURE IN THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF TACHYCARDIAS AND OTHER DISORDERS OF THE HEART BEAT\*

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BOSTON

ONE of the chief uses of the electrocardiogram in clinical medicine is in the differential diagnosis of cardiac arrhythmias. Ordinarily, a definite diagnosis of the disorder of the beat can be made easily from the standard leads, but in patients with tachycardias it may be difficult or impossible to be certain of the type of arrhythmia present because the auricular waves may be small or hidden in the QRS or T complexes. The same statement is occasionally true with slower rates. Hence, a lead in which the electrodes are so applied as to show maximal potential changes developed by auricular activity may be of help under such circumstances.

Lewis<sup>1</sup> first noticed in 1910 that the F waves of auricular fibrillation were best brought out in electrocardiograms in which the exploring electrodes were placed over the region of the right auricle. Later, Ackermann<sup>2</sup> demonstrated that the auricular waves were well defined when needle electrodes were placed in the second and fifth interspaces to the right of the sternum. Subsequently, many studies have been made, many of which have dealt with distinguishing the activity of the two auricles, a problem with which we are not here concerned. Luisada<sup>3</sup> has summarized knowledge of auricular leads and of auricular disorders. Among these studies an important advance was made in 1934 by Lieberman and Lieberman,<sup>4</sup> who introduced the technic of the esophageal lead. This has been utilized frequently since then for auricular disorders but especially in the diagnosis of posterior myocardial infarction. Recently, Butterworth and Poindexter<sup>5</sup> have em-

phasized the value of the esophageal lead in clinical electrocardiography in the diagnosis of tachycardias and arrhythmias.

In January, 1937, the employment of a special auricular lead was first introduced at the Boston City Hospital by one of us (J M F). In the succeeding ten years this lead has been routinely employed, often in combination with carotid-sinus pressure, when the type of rhythm was not clear. During this period the procedure has been carried out about 2600 times, which represents 4.3 per cent of the total of 60,000 records taken. Our procedure has consisted in taking electrocardiograms by the usual technic including routine precordial leads. In addition, we have obtained the special auricular lead by removing the electrode from the left arm and placing it on the chest in the third interspace just to the right of the sternum. Tracings are then taken with the control switch successively at Leads I and 3. This has given records that are CR and inverted CF (labeled in the illustrations as CF'). It has been found that the auricular waves are seen best sometimes in one and sometimes in the other lead. Since we have not been concerned in this lead with the details of contour of the P waves or other complexes, the inverted CF lead has been no disadvantage and technically has been a more rapid and simple procedure than a CF lead taken in the conventional way.

In addition, while these leads are being taken pressure has been applied alternately to the right and left carotid sinuses or to both at once. Although it is well known that such vagal stimulation may abolish certain paroxysmal tachycardias or produce a temporary increase in auriculoventricular block in auricular flutter and tachycardia, thus making it easier to make an electrocardiographic diagnosis, it seems to be less widely appreciated that this maneuver may cause a very slight transitory slowing in

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patients with normal heart rates, both with sinus rhythm and with arrhythmias. In such cases, in which the P wave may have been hidden in the preceding T wave or in its own QRS or T complexes,

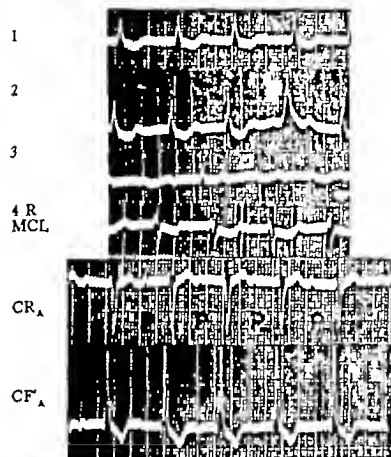


FIGURE 1 Normal Sinus Rhythm with Prolonged Auriculo-ventricular Conduction Time

The P waves are not definite in the usual leads but appear clearly in  $CR_A$ , as well as in  $CF_A$

the transitory slowing thus produced may uncover the hidden P wave

The procedure has been employed in all obscure cases, especially in those with tachycardias of any

dependent auricular rhythm in this lead has been strong evidence in its differentiation from other conditions giving similar electrocardiographic patterns. The auricular waves of auriculoventricular nodal rhythms have also been frequently clearly

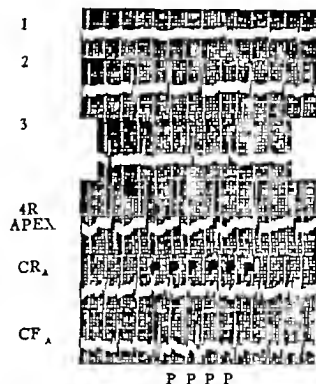


FIGURE 3 Auricular Flutter, with Varying Auriculoventricular Heart Block

The P waves are made out with difficulty in the usual leads but are clearly shown in both  $CR_A$  and  $CF_A$

brought out, and the method has been useful in the differentiation of such rhythms from auricular fibrillation with complete heart block.

Figures 1 to 6 illustrate the value of the lead in some of these disorders of the beat

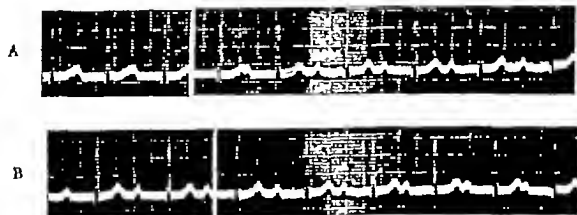


FIGURE 2. Continuous Record of Lead 2 Only

Incomplete auriculoventricular block with P waves superimposed on preceding T waves. A shows an electrocardiographic tracing when carotid sinus pressure is applied and B a tracing when pressure is released. Carotid sinus pressure produces moderate slowing thus separating the T and P waves and enabling a diagnosis to be made

type. In particular it has been of value in auricular flutter with 2:1 block. It has also been of great help in the diagnosis of paroxysmal ventricular tachycardia, in which the demonstration of an in-

The technic is simple, can be carried out quickly and produces no discomfort for the patient. It is thus suitable for routine employment in clinical electrocardiography. Through its use correct diag-

noses have been made early, and proper treatment instituted promptly Other special leads that have clinical electrocardiography, we have found that the third-right-interspace lead has made it unnecessary

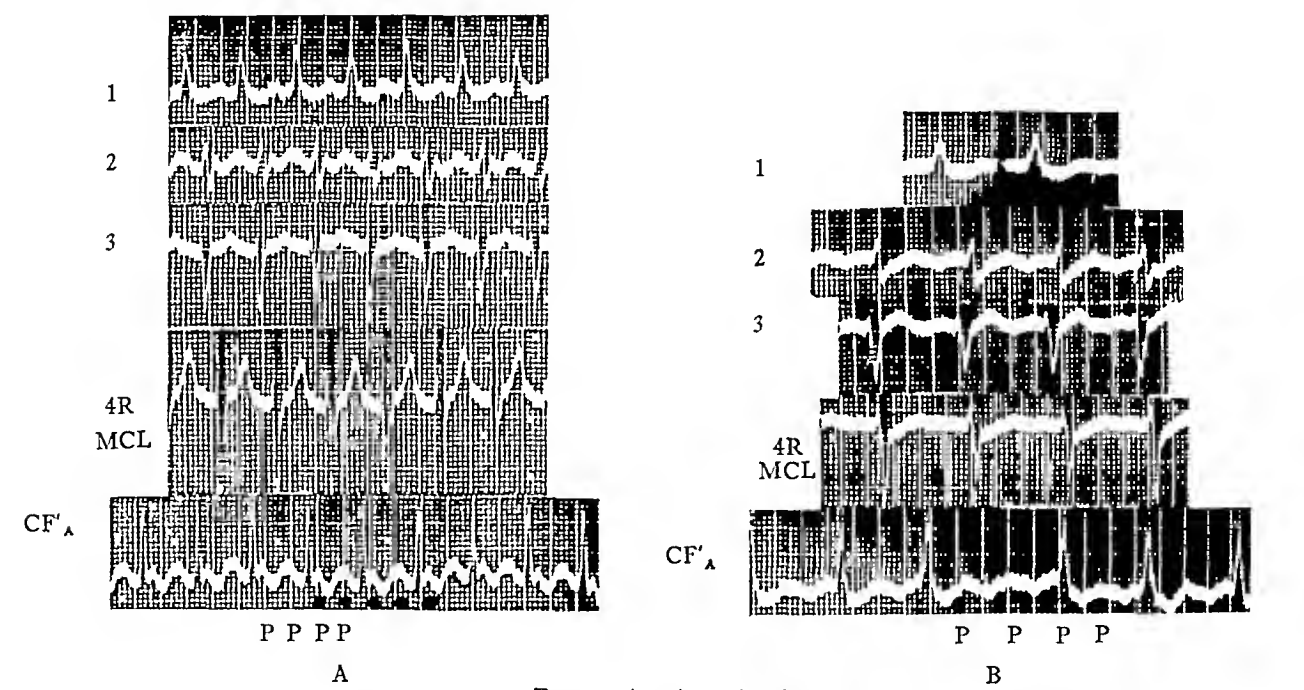


FIGURE 4 Auricular Flutter  
The first record (A) shows 2:1 heart block with P waves at a rate of 286, much more easily made out in CF<sub>A</sub> than in the standard leads. The second record (B), after quinidine, shows the persistence of flutter with a slower auricular circus movement (172) that can be conclusively diagnosed only in CF<sub>A</sub>.

been used for this purpose, in particular the esophageal lead, involve a much more formidable pro- to resort to the esophageal lead except in very rare cases  
The standard texts on electrocardiography occasionally mention special leads for bringing out the

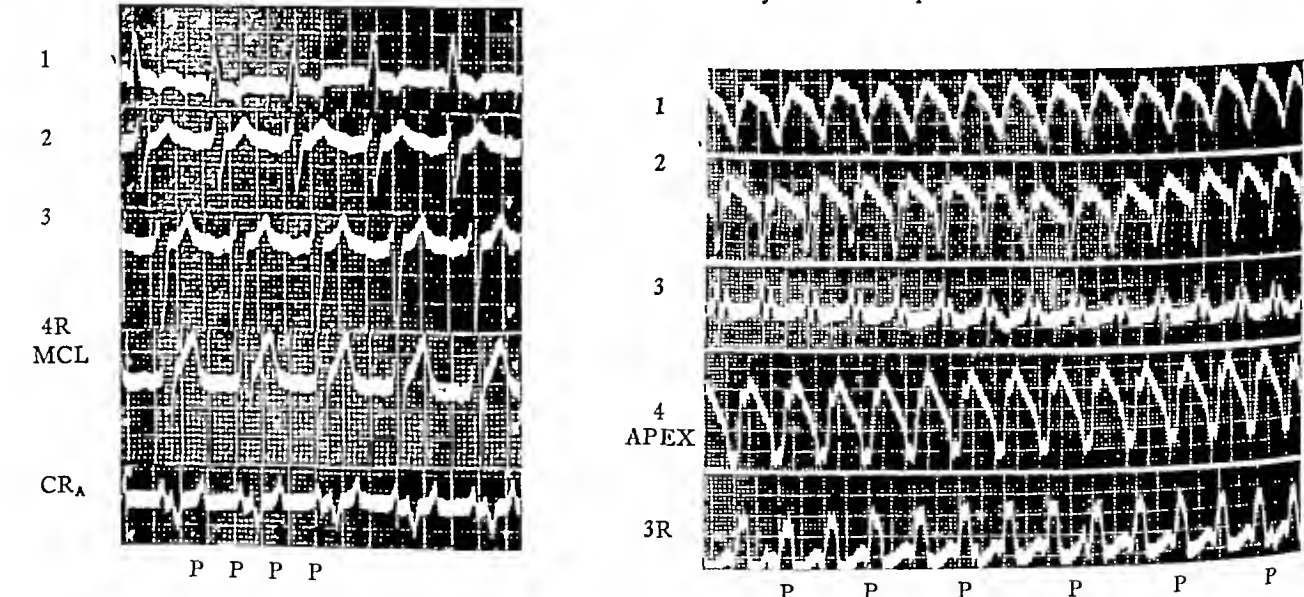


FIGURE 5 Paroxysmal Auricular Tachycardia with 2:1 Heart Block  
Auricular rate, 214, ventricular rate, 107. Diagnosis can be made only in CR<sub>A</sub>.

FIGURE 6 Paroxysmal Ventricular Tachycardia (Rate, 154)  
The independent auricular rhythm at a slower rate (64) can be made out only in the auricular lead, CR<sub>A</sub> (labeled 3R).

cedure Although the esophageal lead is probably, the best for the elucidation of auricular activity in P waves The discussion, however, is usually confined to a single arrhythmia such as auricular flutter

and is easily overlooked, and the wide usefulness of the lead is not emphasized. It is certainly clear that the majority of physicians who are doing electrocardiography are unaware of the value of this procedure. Whether the conventional CR<sub>1</sub> or CF<sub>1</sub> would reveal as much information concerning auricular activity as the auricular lead is not evident from this study, since such leads have not been taken continually in this laboratory.

### SUMMARY

A special electrocardiographic lead that has proved of value in the identification of auricular activity is described. This consists of the placement of the left arm electrode over the third interspace

to the right of the sternum and taking the electrocardiographic tracings successively in Leads 1 and 3. At the same time the application of carotid-sinus pressure is carried out. This procedure is useful in routine clinical electrocardiography in the diagnosis of tachycardias and of other arrhythmias when the P waves are not readily evident.

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## MEDICAL PROGRESS

### DIABETES (Continued)

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#### Metabolic Changes

Clinical reports as well as chemical studies emphasize certain new features in diabetic acidosis. The case report of Holler<sup>12</sup> showed that it is possible for a patient in diabetic acidosis to develop a critically low level of potassium in the blood serum, with paralysis of respiration that may be relieved by the administration of a potassium-containing solution.

Martin and Wertman<sup>14</sup> have analyzed serial measurements of the serum potassium, magnesium and calcium concentrations in 14 patients with diabetic acidosis (carbon dioxide combining power below 9 milliequiv. per liter). Three patients were comatose on admission, 3 were semicomatose, and 8 were conscious, 1 patient, admitted in coma, died. In addition to the electrolytes mentioned above, serum sodium, total protein, blood sugar, carbon-dioxide combining power and nonprotein nitrogen were determined on every patient, reaction, albumin-globulin fractionation and serum inorganic phosphorus determinations were made on a few patients.

In addition to the usual findings of acidosis, hyperglycemia and hemoconcentration, fluctuations in the serum potassium, magnesium and phosphorus concentrations were observed during the course of therapy. The serum potassium was above 6 milliequiv. per liter in the 5 patients on whom the determination was made on admission, the highest being 10.3 milliequiv. During therapy, the serum potassium was usually diminished within the first twenty-four hours and frequently fell to very low values (1.9 and 2.18 milliequiv. per liter). The potassium concentrations usually returned to normal levels within two or three days.

The serum magnesium, which was determined in 5 cases on admission, was slightly elevated in 2, normal in 2 and slightly below normal in 1. In most patients the serum magnesium fell at some time to abnormally low values, and then gradually rose. There was a rough correlation between the state of consciousness on admission and the serum magnesium concentrations.

Serum calcium concentrations were generally normal, although the total circulating calcium may have been reduced owing to the hemoconcentration.

The serum sodium concentration was either normal or somewhat low on admission, but soon after therapy was begun came into the normal range.

Inorganic phosphate determinations were made on only 2 patients, and in both the changes correlated with the serum potassium and blood sugar levels during therapy, which in all patients consisted in

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varying amounts in physiologic saline solution, one sixth molar sodium lactate, 5 per cent glucose, plasma and insulin

Martin and Wertman<sup>14</sup> point out the similarity between the marked muscle weakness shown by several of the patients and that seen in familial periodic paralysis, another condition associated with low serum potassium concentration

Holler et al<sup>15</sup> have described patients who developed a similar syndrome during therapy for diabetic acidosis or coma. Therapy with potassium produced dramatic improvement

In interpreting the changes in serum potassium concentration, Martin and Wertman<sup>14</sup> mention possible changes in urinary excretion or use of the potassium in carbohydrate metabolism. Since magnesium is, like potassium, nitrogen and phosphorus, an important intracellular component, it is not surprising to find that the movement of magnesium follows that of the other three compounds. However, as the authors point out, until intracellular concentrations of these substances are known it will be difficult to interpret adequately changes in serum concentration. Atchley et al<sup>16</sup> showed that with the negative nitrogen balance that occurred in diabetic patients after the withdrawal of insulin, a negative phosphorus and potassium balance could be demonstrated as well. One might, by combining the data of Martin and Wertman with that of Atchley and his associates, assume that there is an intracellular depletion of potassium with increased serum concentration and loss in the urine during the period of insulin lack. On administration of insulin, the reverse would be true, but because of the potassium loss in the urine a body deficit exists, thus reducing the serum potassium concentration. If this interpretation is correct, the administration of potassium as therapy is called for, as the authors suggest

The warning given by the authors against the administration of potassium to diabetic patients in shock is well taken, and, in fact, one might even say that potassium should be administered only very cautiously, or not at all, until adequate urinary output has been established. Several reports of dangerously high blood potassium concentrations have been published and have been added to and reviewed by Finch, Sawyer and Flynn.<sup>17</sup> It is especially noteworthy that a flaccid paralysis resembling that seen with low serum potassium may result from potassium intoxication

Errebro-Knudsen<sup>18</sup> studied two healthy male medical students to determine the effect of intense muscular exercise on ketone-body formation. Both were trained sportsmen and trained for two months in riding on the bicycle ergometer so that they could perform work at about 1100 mkg a minute for upward of three hours and forty minutes — this is really exhausting physical work

For three days before the first experiment they lived on a mixed diet and then determinations were made. The second experiment was carried out after two days on a diet rich in fat and poor in carbohydrate. Thus, the total calories were between 3000 and 4000 for each diet. On the high-fat diet the figures were 57 gm of carbohydrate, 30 gm of protein and 398 gm of fat. The students weighed 74 kilograms and 67 kilograms, respectively. On a mixed diet the total ketone bodies during work rose very slightly, from 0 in one experiment to 2.4 mg per 100 cc. On one day the values started at 5.2 mg and fell to 3.5 mg at the end of the work period. Measurements were also made during the period following cessation of the exercise, and in each case a striking increase in ketone bodies occurred from three to twenty-three minutes after the end of the exercise. The values rose from 4.5 to 11.1 mg. per 100 cc as an example. The respiratory quotient rose during the period of actual exercise from 0.78 to 0.84 and then fell back to 0.78, but declined perceptibly to 0.70 during the fifteen to twenty minutes following the cessation of exercise. In the next twenty minutes it rose to 0.74. It seemed evident, therefore, that with the cessation of muscular exercise the fuel utilized changed from carbohydrate to fat. However, it also shows that the low respiratory quotient was due to an oxidation of lactic acid accumulated during work. This could be explained by a retention of carbon dioxide

The students who had been on a low-carbohydrate, high-fat diet started with respiratory quotients of 0.69 and 0.73. During work a rise in respiratory quotient to 0.73 in 1 and 0.77 in the other took place. The increase in blood acetone values was studied throughout the work period from 6 in one case and 12 in the other to 8 and 15 mg, respectively, with a further increase during the resting period up to 13 and 24 mg per 100 cc, respectively. The blood sugar values showed only a slight decline in all the experiments from about 80 mg to 54 mg per 100 cc in the experiments on a high-fat diet, with a much slighter decline in the experiments on a mixed diet

One of the reasons for undertaking these experiments was to determine whether or not the fatigue experienced on a high-fat diet is really due to the accumulation of ketone bodies. The change in concentration of ketone bodies was so slight at the end of the work period as to lead to the conclusions that the fatigue is not due to ketone bodies

#### HYPERGLYCEMIC ACTION OF HIGHLY PURIFIED ALKALINE PHOSPHATASE

Professor William Kerppola, of Helsinki, Finland, was kind enough to provide the following abstract of his recent work, *On the Hyperglycemic Action of Highly Purified Alkaline Phosphatase*, which is now in press

Highly purified alkaline phosphatase has been prepared from fresh cow udders. The strength of this preparation exceeds about five thousand times that of the first basic solution and contains about 35,000 active units (Alberts) in 1 cc. This amount may be capable of liberating about 20 gm. of glucose.

The preparation can be injected into animals and human beings without any local or general reaction. The blood picture remains unchanged.

When phosphatase is injected intravenously in rabbits during fasting the blood sugar increases suddenly and receives its highest value in an hour. Afterward it stays at an even height for about five hours and then decreases rather abruptly during the next two hours and comes gradually back to its initial value. No sugar was observed in the urine — not even when the blood sugar values were high. If phosphatase is injected subcutaneously in rabbits the blood sugar value remains unchanged but increases suddenly after seven to nine hours. The blood sugar value falls rather quickly and returns to the initial level in four to six hours. If a phosphatase is injected continuously once a day the blood sugar remains elevated as long as the treatment is continued.

If a glucose-tolerance test is made on rabbits during the phosphatase treatment, and if the curve obtained is compared with a corresponding one obtained without this treatment, a substantially raised and prolonged curve may be noted in most of the phosphatase-treated animals.

The decrease of the blood sugar value in rabbits produced by insulin injections is, under the influence of phosphatase, distinctly smaller than that in non-treated animals.

The glycogen values in the liver and the muscles of the treated animals do not differ from those of the nontreated animals.

The action of alkaline phosphatase on blood sugar seems to be quite the opposite of that of insulin.

#### CONVULSIVE STATES IN DIABETES

Convulsive states in diabetes are frequently encountered. The differential diagnosis is often difficult because in younger patients epilepsy is not uncommon. It was observed in 50 cases at the George F. Baker Clinic among children, and these were proved with abnormal electroencephalograms. The following opinion was expressed by Dr. Priscilla White<sup>11</sup>:

Hyper and hypoglycemia have been suspected as causes. It is possible that hypoglycemia merely reveals the latent case. A few cases have had serious progression. More have apparently subsided with sedation therapy which has been followed with improvement in electroencephalographic tracings. Of some interest is Case 15322 whose similar twin does not have diabetes. The electroencephalograms reveal similar deviations from the normal. The diabetic has epileptiform attacks in the absence of hypoglycemia. The non-diabetic twin has had none.

In a preceding edition from the same clinic Dr. Howard F. Root<sup>12</sup> reported the autopsy findings in 2 cases.

Case 7089 developed diabetes in March, 1920 at the age of two years and three months. Feeble-mindedness and epilepsy were evident at the age of eight years and she died in a convulsion at the age of twenty years. The histological diagnosis after examination of the brain was retarded development of the cortex, cerebellar degeneration (granular layer) and degeneration of the islands of Langerhans. For a detailed account of this patient see Case 2 in the paper of Ross and Dickerson. Case 11499 developed diabetes at the age of 43 years and epilepsy at 48 years. He died of bronchopneumonia caused by aspiration of food during a convulsion. In these 2 cases the marked mental deterioration during life and the extensive pathological changes found in the brain at autopsy suggested some congenital cause or at least damage to the brain produced by some other cause than hypoglycemia.

Ellenberg and Pollack<sup>13</sup> have discussed the problem with detailed reports of 2 cases and with the results of pathological examination in 1. Each patient had uncontrolled diabetes and showed repeated hospital admissions for ketosis or insulin reactions, and in the fatal case detailed study of the brain was made, resulting in the diagnosis of degenerative encephalopathy of unquestionably toxic origin.

Sections of the frontal lobe, stained with hematoxylin-eosin disclosed several arachnoid cell clusters in the leptomeninges. The nerve cells of the cortex presented a diversity of degenerative changes. Some were markedly swollen many however, were shrunken and contained pyknotic nuclei while some contained finely granular, deeply staining oval nuclei with an occasional enlarged nucleolus. There were other cells in which it was difficult to distinguish nucleus from cytoplasm. The outline of some cells was irregular and occasionally the cytoplasm was poorly defined. Satellitosis was increased. With Nissl stains marked central chromatolysis was seen in some areas. The Nissl substance itself was usually finely granular diffusely scattered through the cytoplasm or concentrated at the periphery at the base of the cell. Some cells stained very faintly. Both cortex and subcortex showed marked and diffuse gliosis. The blood vessels were engorged. Similar though less marked changes in the nerve cells were seen in the tegmentum pons and medulla.

In the second case dilantin, phenobarbital and tridione were each tried in full therapeutic dosage, with no measurable beneficial effect on the frequency or severity of the attacks.

An electroencephalogram made in April, 1947 again showed alpha waves with frequencies as low as 7.5 per cent with rare bursts of 6 per second activity and some single 3 per second waves. Hyperventilation did not increase the amount of slow activity. A record taken 10 minutes after the intravenous injection of 50 cc. of 50 per cent glucose showed the same characteristics.

In their discussion the authors suggest several possibilities the convulsive seizures are the manifestations of irreversible cerebral changes following repeated attacks of insulin hypoglycemia, the changes are independent of the diabetes and are actually an influence in the causation of repeated shocks, the attacks are evidence of coincidental epilepsy. They cite the possibility suggested by Greenblatt, Murray and Root that the cerebral changes are independent of the diabetes and insulin hypoglycemia and actually instigate the frequent reactions, because abnormal electroencephalograms

were encountered in 51 per cent of the problem patients with diabetes. The frequency of actual epilepsy in patients with diabetes provides a most complicating factor, and all peculiar insulin reactions should be studied with this possibility in mind.

#### ELECTROCARDIOGRAPHIC CHANGES

Changes in the electrocardiogram in diabetic acidosis have been described consisting of depression of the ST segment, lengthening of the QT interval and alternation in the T waves. The reversibility of these changes in a short period has suggested that changes in the electrolyte gallop were important factors in causing abnormalities. Martin and Wertman<sup>22</sup> studied 12 patients who entered the hospital in severe acidosis with the carbon dioxide combining power of the blood under 9 milliequiv per liter. Chemical determinations in all cases included serum calcium, potassium, sodium and magnesium levels, total plasma protein, blood sugar and carbon dioxide combining power. Sagging of the ST segment was a prominent feature when acidosis was marked, but it usually disappeared within twenty-four hours. In 19 cases of such depression of the ST segment the reaction or the blood carbon dioxide was low in 16. There was no correlation in this series between these changes and the serum potassium level. Thirty-seven records showed prolonged QT intervals, many of these occurring one to four days after intensive therapy had been started. Sixteen of these were associated with low total or ionized serum calcium or potassium, but in 21 records, that is, 57 per cent of the patients whose records showed prolonged QT intervals at normal levels of serum calcium, a high degree of correlation between low T waves and low serum potassium levels was observed. In explanation of these changes the authors point to the various factors that may be present: the relation between extracellular and intracellular electrolytes, cardiac nutrition as affected by low insulin levels and the effects of anoxia and nitrogen retention. Actually the reaction values were as low as pH 7.28, 7.05 and 7.12 in 5 cases studied, but the remainder of the series did not have a determination of the reaction. Low levels of serum potassium included one of 1.9 and others as low as 2.18 and 3.2 milliequiv per liter. In 11 cases with potassium levels under 4.2 milliequiv per liter 9 showed low or isoelectric T waves. It is well known that with high potassium levels in the blood serum high T waves may occur. With higher levels of serum potassium, depression of the ST segment will occur, and actual intraventricular block occurs at the level of 10 milliequiv and final cardiac arrest at 14 to 15 milliequiv per liter.

The study emphasizes, however, the temporary character of these changes when adequate treatment for diabetic coma is given.

#### ARTERIOSCLEROSIS

In 1928 Joslin<sup>23</sup> wrote as follows:

The diabetic lives and dies in the arteriosclerotic zone. Lives in it because two-thirds of the 4592 true diabetics in the present series originated after 39 years of age, dies in it because although the average age at death of 339 cases in the Naunyn Period was 44.8 years, the average age at death of the 607 fatal cases in the present Banting Epoch is 54.2 years, and for the last year's 60 fatal cases was 59 years. During 1925 of all the diabetics who died in Massachusetts 86 per cent were above the age of 50 years. This is the year of age in which diabetes develops most frequently for men, the most common quinquennium for both sexes being between 49 and 53 years.

Today diabetic coma having dropped to 3.1 per cent as a cause of death, the duration of the disease having increased from 4.9 to 14.1 years, and the average age at death of the diabetic cases having risen to 64.5 years, it is not surprising that cardiovascular disease causes 66.6 per cent of diabetic fatalities. A generation ago diabetic patients did not live long enough to contract hardening of the arteries.

Despite the mounting incidence of arteriosclerosis in diabetes, our group is decidedly not pessimistic. Over a generation ago, when diabetic coma claimed 63.8 per cent of our cases, we acknowledge that we felt it represented the culmination of the disease and was the act of God, but we learned our mistake five years before insulin was discovered. Today we do not believe that arteriosclerosis represents the end of the diabetic patient either in consequence of the disease or as a coincident complication. We are firmly convinced that on the whole our patients who know the most, have followed treatment most assiduously and have received from our hands what we consider our best methods of treatment not only have done the best but also show the least number of arteriosclerotic lesions. We may not have more than 8 per cent of children, as studied by Dr. Priscilla White and later reported in this review, who are free of the disease after twenty years, but we do have a few cases of severe diabetes at the very onset in children who remain free from arteriosclerotic lesions after twenty-five years of diabetes. The recovery from impending coma by Nathaniel Potter, founder of the Sansum Clinic, in 1917 led the way to other recoveries from diabetic acidosis, and we are confident, as time goes on, that the medal, which the Diabetic Fund has created for patients with diabetes of twenty-five years' duration without evidence of degenerative disease in eyes, vessels and kidneys, will eventually be granted to many patients throughout the world. Today, the question is not so much the appalling incidence of arteriosclerosis in diabetes of long standing but what patients and doctors are going to do about it.

Substantiation of the studies of Root, Bland, Gordon and White<sup>24</sup> in their comparison of the



incidence of coronary disease and angina pectoris in nondiabetic and diabetic persons has been furnished by Stearns, Schlesinger and Rudy,<sup>28</sup> whose conclusions are as follows

Functionally significant coronary artery disease was disclosed in approximately three fourths of the hearts of 50 diabetic patients by means of postmortem injection plus dissection technic. One third of these patients had died of acute coronary heart disease. One quarter of the entire group had had angina pectoris. Among diabetic women over the age of 40 the incidence of significant coronary arteriosclerosis of angina pectoris and of death due to coronary artery disease is as great as among diabetic men. This is in sharp distinction to the sex difference in these respects in the non-diabetic population. Angina pectoris,

— by establishing criteria. As indexes of control, coma, hyperglycemia, hypercholesterolemia and hepatomegaly were utilized. The results are shown in Table 7. Thus, the frequency of coma was only 17 per cent in the patients little affected with arteriosclerosis, 38 per cent in those moderately affected and in 70 per cent of those who were incapacitated. The following are the conclusions of the article

Whereas 8 per cent of 200 survivors were free from vascular lesions 92 per cent had them.

These statistics are the worst possible because they did not have modern diabetic therapy for 50 per cent of their

TABLE 7

TYPE OF PATIENT	NO. OF CASES	PATIENTS WITH COMA PERCENTAGE	HYPERGLYCEMIA* PERCENTAGE	HYPERCHOLESTEROLEMIA† PERCENTAGE	HEPATOMEGALY PERCENTAGE
Normal and retinal sclerosis only	28	1	28	25	0
Moderately affected by vascular disease	114	38	50	54	22
Incapacitated by vascular disease	50	74	54	47	36

\*Blood sugar of 40 mg. per 100 cc.

†Blood cholesterol of 250 mg. per 100 cc.

deaths due to acute coronary disease and congestive heart failure all are more common when hypertension is present in diabetic patients than when the blood pressure is normal. The severity of the coronary arteriosclerosis is correlated with the duration but not with the severity of the diabetes. Early detection of the symptoms of coronary artery disease in persons with diabetes is necessary if the sequelae of coronary arteriosclerosis are to be postponed or avoided. Mild hyperglycemia is preferable to a regimen which may result in insulin hypoglycemia and the attendant risk of precipitating myocardial infarction.

The relation of vascular disease to diabetes in childhood has been investigated by White.<sup>29</sup> Of 350 patients whose onset of diabetes occurred under fifteen years of age and who had survived twenty years or more of diabetes, 200 were examined in detail after they had had diabetes for twenty years or were known to have had arteriosclerotic lesions prior to the twentieth year of the disease. These patients are actually young adults. One hundred and ninety, or 95 per cent, are between the ages of twenty and thirty-nine years, and 10, or 5 per cent, were over forty. The sex distribution was even. Eight per cent of the patients were Jewish. The peak of age of onset was younger by seven years than it is in our entire juvenile series — namely, five years of age, compared with twelve years in all patients.

The total incidence of a vascular disease was demonstrated in 184 cases or 92 per cent. The lesions were as follows: cerebrovascular disease, 2.5 per cent, coronary insufficiency, 8 per cent, hypertension, 40 per cent, nephritis, 50 per cent, calcified arteries, 75 per cent, retinal hemorrhages, 80 per cent, and retinal sclerosis, 85 per cent.

One must refer to the original article for details, but in the course of this review Dr. White made a very definite contribution to an estimate of the control of diabetes — as contrasted to lack of control

diabetic lives. And unfortunately, comparison of patients treated with modern methods cannot be made until 1950 for it requires 15 years of diabetes for vascular lesions to become manifest to the clinician. Protamine zinc insulin was introduced into this country in 1935.

Poor control of diabetes paralleled the severity and frequency of the lesion.

Particularly notable in this study was the demonstration that pelvic arteriosclerosis was common and especially that it was of prognostic import for the fetus in pregnant patients with diabetes. Dr. Joseph H. Marks, roentgenologist at the New England Deaconess Hospital, permits me to state that in a study of 75 nondiabetic young women under forty years of age (a comparable age group to Dr. White's series), he found calcified pelvic arteries in only 1 case. And Dr. Marks also allows me to add that all but 1 of 19 cases of calcification of the vas deferens occurred in diabetic patients.

Dolger<sup>37</sup> studied 200 patients with diabetes of twenty-five years' duration, and among these there was not one who escaped vascular damage as shown by retinal hemorrhages and albuminuria or hypertension, or both, in varying degree.

The group investigated consisted of 16 whose age of onset of diabetes was below 10 years, 39 whose age of onset was between 10 and 20 years, 22 between 20 and 30 years, 43 between 30 and 40 years, and 80 between 40 and 50 years. Retinal hemorrhage was the predominant lesion when diligent search was made routinely, and it often preceded the appearance of albuminuria and/or hypertension. All three lesions appeared in the patients regardless of the age of onset or degree of severity of the diabetes, the need for insulin, the type of diabetic "control" or diet employed, the blood cholesterol levels, or the absence of x-ray evidence of arterial calcification.

Every diabetic would seem at present to be doomed to the inexorable development of vascular damage despite the benefit of insulin in prolonging life. At most, 25 years of freedom from arteriosclerosis can be offered even to the juvenile diabetic.



In a subsequent article Dolger<sup>28</sup> pointed out that "Careful scrutiny of the retina of each patient over the course of years indicated that the earliest clinical manifestation of vascular damage can be found in the eye." In the discussion that followed he reported that vitamins C and P, rutin and hesperidin did not influence retinal hemorrhages significantly because of spontaneous remissions and exacerbations displayed by these lesions, and he considered that work being done with cytochrome C or related oxidized enzymes was far more provocative and pertinent than vitamin research. The usefulness of determinations by capillary fragility proved, in his hands, so variable as to be valueless, being positive one day, negative in twenty-four hours and positive again a week later.

It is the impression of Dr. Priscilla White, who has followed the progress of our cases of retinitis proliferans, especially in young diabetic persons, that there has been much less rapid progress of these lesions since the introduction of rutin. Further-

since 1917, 42 are known to have died during 1946, the average age at death being 60.6 years and the duration of diabetes being 13.1 years. Coronary thrombosis was responsible for 11 deaths, carcinoma for 7, cerebral thrombosis or hemorrhage for 6, diabetic coma for 4, and congestive heart failure due to hypertension or arteriosclerosis for 3, with intercapillary glomerulosclerosis, rheumatic heart disease, pyelonephritis and uremia, traumatic fracture of the spine, gangrene of the leg, tuberculosis of the lung, Addison's disease and xanthomatosis of the liver (primary) accounting for 1 each.

Only 3 juvenile diabetic patients were known to have died. Autopsy on 2 revealed extensive intercapillary glomerulosclerosis, and the clinical picture in the third led to the same diagnosis before he left the hospital to die elsewhere a few months later.

Vascular degeneration, so evident, remains the greatest challenge to the physician treating diabetes today. It is our incentive for insisting on rigid diabetic control in our patients.

TABLE 8 Control of Diabetes with Separate Injections and with Mixtures

TYPE OF DIABETES	RESULTS	SEPARATE INJECTION	SYRINGE MIXTURE	BOTTLE MIXTURE
		%	%	%
Adult	{ Excellent	33.0	34.9	50.0
	{ Good	51.0	44.9	36.1
	{ Poor	16.0	20.2	13.9
Juvenile	{ Excellent	15.8	15.5	36.0
	{ Good	55.6	49.1	36.0
	{ Poor	28.6	35.2	28.0

more, she has not noted the wide variations of capillary fragility observed by Dr. Dolger. Dr. Howard F. Root, who especially has been concerned with the use of rutin in our entire clinic, substantiates her opinion.

At the Mason Clinic in Seattle during 1946, Palmer<sup>29</sup> reported 236 patients seen for the first time. The average age was 49.8 years, and the average age at onset 44.2 years. Among the new adult patients degenerative diseases were very common. Thus, 41 per cent had hypertensive or arteriosclerotic heart disease, whereas of 429 diabetic patients admitted to the hospital, including the 236 new cases in the outpatient department, hypertensive and arteriosclerotic heart disease was present in 61.6 per cent. There was 1 death from diabetic coma among the 13 cases of acidosis treated, and of the 13 diabetic patients who were pregnant, 8 were delivered by cesarean section between the thirty-fifth and thirty-eighth weeks, resulting in 8 living children, in the remaining 5 cases, 3 infants were delivered spontaneously, 1 was stillborn and the other 2 died during the neonatal period. There was a miscarriage at thirteen weeks and a therapeutic abortion at five months because of the presence of uremia in the mother. Of the 2813 patients with diabetes followed at the Mason Clinic

In a subsequent article Palmer<sup>30</sup> reports favorably upon the use of insulin mixtures (Table 8). It is obvious that the ideal mixture has not been discovered, and in general it seems desirable for physicians to decide on the method of treatment of their patients with protamine-zinc insulin, separate injections of regular insulin or crystalline insulin and of protamine-zinc insulin, a mixture in the syringe, or premixed in a bottle, rather than to attempt the use of all four methods, which would almost certainly result in confusion. If physicians will only be patient for a year or two, undoubtedly new methods for the use of insulin will be found.

Campos and Molina,<sup>31</sup> in Buenos Aires, observed 25 consecutive cases of diabetes at all ages and reported on the fundus oculi. All these patients were poorly treated over a long period, and the most frequent combination was hypoalbuminemia, hypocholesterolemia and diabetic retinopathy. This combination appeared in 11 out of the 25 cases.

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 34131

#### PRESENTATION OF CASE

A twenty-two-year-old linoleum layer was admitted to the hospital because of red urine.

Two months before admission, following a football game, he developed a sore throat accompanied by epistaxis and occasional biting of the tongue while asleep. Following this episode, which lasted an unstarred period, he returned to work but was easily fatigued and slept a great deal. Three weeks before entry he again had severe epistaxes, sore throat and malaise. He had to leave his job on several occasions because of fatigue and drowsiness. During this period he developed red urine and was sent to another hospital, where he was catheterized because of inability to void. Thirty-two ounces of urine was obtained. While there he had a generalized convulsion. One day before transfer to this hospital he was again catheterized because of continuing retention. The face, neck, and eyelids were edematous. He was treated with penicillin.

The patient had been an apparently normal child. At the age of six he developed enuresis. Repeated attempts to break him of this habit were unsuccessful. Urine was frequently analyzed but found to be normal. The enuresis persisted until two years before entry, when he married. Since then he had averted difficulty by getting up to void during the night. At the age of eight he had an appendectomy, and at ten the tonsils and adenoids were removed. At thirteen he was found to have an abdominal tumor. Examination revealed a distended bladder.

A suprapubic cystostomy was performed, and no abnormality was found. The discharge diagnosis was "Distended bladder—retention of urine." About three years before entry he was rejected from the Army because of a "spina bifida." During the past two years he was noticed to limp to an increasing degree.

Physical examination revealed a very pale man in extremis. The breath was uremic. He had generalized twitching of the arms and a positive Chvostek sign. The skin was dry, and the neck veins were prominent. Examination of the fundi was negative. There was clotted blood in the nose. The apex of the heart was at the anterior axillary line, and there was a Grade III systolic murmur heard over the whole precordium but loudest at the pulmonic area. The chest was clear except for widely heard rhonchi. There was no ankle edema. There was an abscess in the right buttock. Some atrophy of the right calf muscles was present. There was bilateral pes-cavus deformity.

The temperature was 98.6°F., the pulse 90, and the respirations 14. The blood pressure was 180 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 2,800,000, with 10 gm. of hemoglobin, and a white-cell count of 25,000, with 88 per cent neutrophils and 12 per cent lymphocytes. The blood chloride was 98, and the carbon dioxide 9.1 milliequiv per liter. The total protein was 6.8 gm. per 100 cc., and the nonprotein nitrogen 146 mg. The urine was red and had a specific gravity of 1.010. There was a +++ test for albumin and a + test for acetone. The sediment was loaded with red and white cells and there were rare casts.

One hour after admission the patient had a generalized convulsion, controlled by 15 gm. of calcium levulinate. He also received luminal, cedilant and magnesium sulfate. He slowly received 1000 cc. of 5 per cent dextrose in water intravenously. He remained in a semicomatose state. An indwelling catheter was inserted, and in one fifteen-hour period drained 1200 cc. of grossly bloody urine. The blood pressure, which had been running about 140 systolic, 70 diastolic, fell to 100 systolic, 55 diastolic, for no apparent reason, and he died thirty-six hours after admission. In the last fourteen hours of life he passed 10 cc. of urine.

## DIFFERENTIAL DIAGNOSIS

DR EARLE M CHAPMAN This is indeed an interesting case and obviously is presented for the diagnosis of the type of kidney disease that led this man to die in rather classic uremia. He was in the hospital thirty-six hours so that very few studies were done.

But the review of the past history and the known facts presented here can lead to a diagnosis of a well recognized entity. I believe that he had a congenital defect — spina bifida — which eventually caused progressive changes in the spinal cord and what might be called a cord bladder. With this he had the other evidence of spina bifida — atrophy of the calf muscles and a bilateral pes-cavus deformity. Evidently through his early life this syndrome was not recognized. We cannot tell from the record, but I doubt it, because if it had been recognized, the patient would certainly not have been subjected to a suprapubic cystotomy unless a congenital valvular deformity, either in the neck of the bladder or in the urethra, was being sought. That this was not an acute process such as acute glomerulonephritis or acute pyelonephritis is indicated by the fact that he had evidence of chronic renal disease. In other words, the heart was enlarged, and he had hypertension, anemia and a fixation of the specific gravity of the urine at 1.010. All these findings indicate the long duration of the disease.

There is one note in the record that I take exception to — that after admission to the hospital an indwelling catheter was inserted and in one fifteen-minute period 1200 cc. of grossly bloody urine was drained, the blood pressure, which had been running about 140 systolic, 70 diastolic, fell to 100 systolic, 55 diastolic for "no apparent reason." It has been the practice of the Genitourinary Service here that patients with chronic, long-standing obstruction to urinary outflow should not be decompressed rapidly, since removal of large quantities of urine in a short time leads to shock, fall of blood pressure and perhaps anuria. I think this is an example of such a reaction in this patient.

I can add little else. This is a recognized entity, although one has difficulty in finding a clear-cut description of it in textbooks. If the urinary tract had been studied and retrograde pyelograms done, which I judge were not since they have not been mentioned, the examinations would have shown a chronic atonic bladder, hydroureter and hydronephrosis. In this condition the kidneys end up with thin shells of cortex, — usually with some pyelonephritis, — but in this case there was very little evidence of pyelonephritis.

In conclusion, I would say that this man had spina bifida, cord bladder and the other evidence of central-nervous-system damage, and that with this he had an atonic, large bladder, a hydroureter, back

pressure on the kidneys and small, atrophic kidneys, with a narrow rim of cortical tissue, and that he finally died in uremia, which at the end, at least, was not aided by the sudden withdrawal of a large amount of urine from the bladder.

DR H J KOWALSKI I should like to ask Dr Chapman how he explains the fact that the urine had been normal for a number of years. The patient's mother was a nurse and she had taken frequent specimens to a hospital for analysis and they had been consistently normal. Although we believed that this was acute nephritis, there were several features about it that were somewhat confusing. One was the low specific gravity of the urine (1.010). The fact that he had passed bloody urine and had renal failure following a sore throat, with epistaxis, of course, favored acute nephritis. Also, he had a high white-cell count. The terminal event was scanty, bloody urine, which is frequently seen in the end stage of this kind of process. I did not believe that this man died in shock. The blood pressure remained fairly well sustained, the pulse was good, and there were no signs of sweating or evidence in the extremities suggesting shock.

DR FLETCHER H COLBY I should think it was unusual even in the terminal stages of the condition such as you describe to have so much hematuria unless associated with a severe, acute infectious process or some other disease in the kidney. It is true that sudden decompression is not desirable, but the record says fifteen hours, not fifteen minutes.

DR CHAPMAN I misread the record. I shall have to retract that statement.

DR COLBY There is no adequate explanation for the copious hematuria?

DR CHAPMAN That is a puzzling point.

DR ALLAN M BUTLER One sees hematuria with pyelonephritis and pyuria.

## CLINICAL DIAGNOSES

Acute glomerulonephritis  
Uremia

## DR CHAPMAN'S DIAGNOSES

Spina bifida  
Atonic bladder  
Hydroureters  
Atrophic kidneys  
Uremia

## ANATOMICAL DIAGNOSES

*Intradural lipoma of sacral canal*  
*Spina bifida occulta*  
Dilatation and hypertrophy of bladder  
Hydroureters, bilateral  
Hydronephrosis, bilateral  
*Pyelonephritis, chronic (with uremia)*  
Parathyroid hyperplasia, secondary

## PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN Autopsy showed what Dr Chapman predicted. The bladder was tremendous, very thick and markedly trabeculated. There were numerous erosions of the mucosa. It is quite possible that the massive hematuria came from one or more of the mucosal erosions. Both ureters were markedly distended and thickened. There was a marked hydronephrosis, with only a shell of normal cortex remaining (Fig. 1). Not knowing about the spina bifida at that time, we immediately looked for a congenital valve in the urethra or some form of obstruction, but we were unable to find any. We then studied the history a bit more thoroughly and decided that the next thing to do was to



FIGURE 1. Marked Hydronephrosis and Hydronecrosis. The bladder is markedly thickened and trabeculated. (Only a portion of the bladder is in the photograph and it has been superimposed on the mid portions of the ureters.)

examine the spinal cord and the spine. Dr Kubik, will you tell us about that?

DR CHARLES S. KUBIK. There was a spina bifida occulta involving the arch of the fifth lumbar vertebra and all of the sacrum.

Filling the sacral canal was an intradural mass of fat, or lipoma, measuring 5 cm. in length and from 2 to 3 cm. in diameter. This lay posterior to the

spinal cord, which extended to the lower part of the sacral canal and was attached to the tumor by dense strands of fibrous tissue (Fig. 2). A condition such as this is not infrequently associated with spina bifida.

At birth in the normal person the lower end of the spinal cord occupies the lower part of the sacral

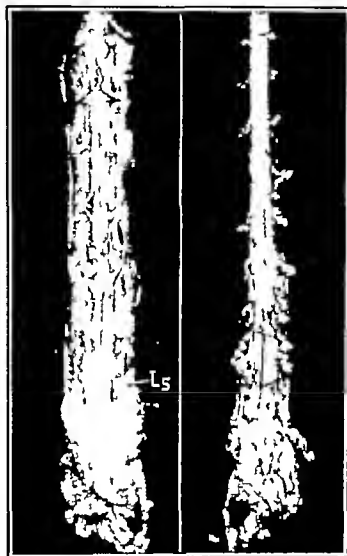


FIGURE 2. Posterior (A) and Anterior (B) Views of the Lower Portion of the Spinal Cord and Intradural Lipoma of the Sacral Canal in a Case of Spina Bifida Occulta.

The lowest visible spinal nerves in the posterior view (A) are the fifth lumbar. Note the upward course of these and other lumbar nerves.

canal. As growth takes place the spinal cord does not increase in length to the same extent as the vertebral column, so that in the adult the cord terminates at about the first lumbar vertebra and the vertebral canal below that is occupied by the spinal nerves of the cauda equina. In this case there was no cauda equina, the tip of the cord was anchored to the lower part of the sacral canal and held in that position as the vertebral column increased in length, with the result that the cord was stretched out and the course of the sacral and lower lumbar spinal nerves was actually reversed.

DR BUTLER. Was there any hydrocephalus?

DR KUBIK. No—and no deformity of the cervical cord or cerebellum. In some cases of spina bifida the medulla and inferior poles of the cere-

bellum may be pulled down into the foramen magnum (Arnold-Chiari deformity), but that was not so in this case

DR J B AYER It would be interesting to know whether the patient had other deformities I suppose he was too sick to find out

DR KUBIK He had clubfeet

DR AYER Was he paralyzed?

DR KUBIK No, but there was some atrophy and the patient had a limp

DR AYER That is consistent with other tumors of this character, with nerves running through the tumor without paralysis

DR KUBIK Signs of pyramidal-tract disease sometimes develop at about the age of puberty, presumably because the cord is stretched as a result of active growth at that time

DR CASTLEMAN Further evidence of long-standing renal impairment was the increased size of the parathyroid glands They weighed over 400 mg (about three times the normal weight) and microscopically showed secondary hyperplasia

DR CHAPMAN What did you find in the kidneys?

DR CASTLEMAN An extensive, chronic, inflammatory process — pyelonephritis, such as one would expect, with a great deal of fibrosis and not much cellular infiltration, which may account for the absence of pyuria

DR KOWALSKI Do you mean that the blood may have come from the bladder? The patient had hematuria three or four days before he entered the hospital

DR CASTLEMAN I still believe it came from the bladder There were no erosions in the ureter or pelves, but there were in the bladder

### CASE 34132

#### PRESENTATION OF CASE

An eight-week-old female infant was admitted to the hospital with a history of jaundice for two weeks and clay-colored stools for one week

The child had been born three weeks prematurely following an uneventful pregnancy Delivery was normal The birth weight was 6 pounds, 12 ounces, and she had gained steadily until the day before admission to 10 pounds, 8 ounces The patient's mother stated that jaundice was noticed for the first time two weeks before admission and then increased progressively One week before admission the stools became clay colored instead of the usual yellow color, but there was no change in bowel frequency or stool consistence During the night before admission the patient became irritable but continued to feed On the morning of entry she vomited orange juice and ceased taking fluids, and the stools became loose, green, and frequent (twenty during the day) The urine was orange colored for the first time In the eight hours previous to entry the

patient had stiffness of the extremities accompanied by frothing at the mouth There had been no cough, hematemesis, melena, bruising or head trauma

Two siblings, five and two and a half years old, were well and had never had jaundice or convulsions

Physical examination revealed an acutely ill, pallid, jaundiced child actively convulsing, with tonic upper extremities and clonic movements of the left leg Anisocoria was present, the right pupil being larger than the left The anterior fontanelle was tense The liver edge was palpated four fingerbreadths below the right costal margin, and the spleen three fingerbreadths below the left costal margin The abdomen felt full, and an umbilical hernia was present There was no purpura, but the tourniquet test was positive

The temperature was 99°F, the pulse 140, and the respirations 45

Examination of the blood revealed a white-cell count of 20,000, with 46 per cent neutrophils, 33 per cent large lymphocytes, 9 per cent monocytes and 12 per cent blast forms The hemoglobin was 8.5 gm The urine was negative for urobilinogen and gave a + test for urobilin A Harrison spot test was positive A digital specimen of stool gave a ++ guaiac reaction The bleeding time was 3½ minutes and the clotting time, 2 or 3 minutes The prothrombin time (after vitamin K therapy for twelve hours) was 13 seconds (normal, 16 seconds) The blood was Group O and Rh— A van den Bergh reaction was 6.4 mg per 100 cc indirect and 1.8 mg direct The total protein was 6.4 gm per 100 cc Lumbar puncture showed an initial spinal-fluid pressure equivalent to 290 mm of water, after removal of 4 cc the pressure was equivalent to 110 mm of water The fluid was orange colored, with 20,000 red cells, 500 white cells per cubic millimeter and a +++ Pandy test. The total protein was 10.40 gm per 100 cc, and the sugar 165 mg per 100 cc A subdural tap on the left was negative, on the right 7 cc of grossly bloody fluid under considerable pressure was removed and clotted on standing An x-ray film of the chest was normal A film of the abdomen showed a liver that appeared to be enlarged The splenic outline was not definitely traced The enlargement of the liver appeared to involve the left lobe

The patient remained in coma, with many convulsive episodes There was no remarkable response to repeated subdural taps or lumbar punctures She was given blood transfusion, vitamin K and parenteral feedings She expired at the end of the second hospital day after a few hours of hyperpyrexia

#### DIFFERENTIAL DIAGNOSIS

DR LEO B BURGIN In summary this eight-week-old infant had a disturbance involving two systems, the central nervous system and the biliary system

I propose to deal with these separately and then, if possible, to relate them.

The conditions commonly causing jaundice during the early weeks of life are icterus neonatorum, congenital syphilis, erythroblastosis fetalis, sepsis and congenital malformations of the bile ducts—that is, atresia.

The history of increasing jaundice, clay-colored stools and orange-colored urine suggests a regurgitation or obstructive jaundice. Bile was found in the urine. Urobilinogen was absent.

Icterus neonatorum is generally considered to be a hemolytic or retention type of jaundice. It occurs in the first week of life. It would hardly be expected to continue as long as eight weeks, nor would its appearance be delayed until six weeks.

Syphilis does not seem likely. The family history was negative. There was no history of sniffles, rash or marked anemia, with or without an erythroblastic picture. Moreover, this baby thrived exceedingly well up to the time of admission. The hepatosplenomegaly and jaundice are consistent, but that is all.

Against erythroblastosis is the fact that the patient was Rh—. The jaundice appeared six weeks after delivery, and there were not the profound anemia and excessive numbers of erythroblasts usually found in the blood smear.

Sepsis with hemolysis might produce this picture. There is, however, no report of fever, although it is possible for infants to have overwhelming sepsis without fever. The elevated white-cell count may have been partially due to dehydration. There does not appear to have been a primary focus for infection unless we consider the diarrhea, which occurred terminally, however, some two weeks after the onset of the jaundice. Finally, the jaundice for the most part was obstructive although there is some evidence of a retention jaundice in the elevated indirect van den Bergh reaction. All in all, the course and history are against sepsis.

We come then to congenital atresia of the bile ducts. In this disorder, jaundice does not appear immediately. There is apt to be a period of two or three weeks before it is noted. In this case, however, jaundice did not appear until the child was six weeks old. It is possible that a slight degree of jaundice went unnoticed for a week or two earlier. Usually clay-colored stools are present from birth, but they may be tinged slightly with bile-stained mucous cells from time to time. Generally, these infants thrive quite well despite the absence of bile for digestion. Certainly, this child did quite well nutritionally almost to the day of death. In considering this diagnosis, I am disturbed by the high level of the indirect van den Bergh reaction. I can only explain it by suggesting that with increasing biliary obstruction the liver cells became functionally damaged and consequently unable to handle the normal daily destruction of red cells.

One other condition that I should like to mention is biliary obstruction from inspissated bile. The only difference from atresia is intermittency of the jaundice. We might infer this from the lack of history of clay-colored stools at the onset.

As for the central-nervous-system disturbance, the evidence presented points to subarachnoid hemorrhage as well as subdural hemorrhage. The presence of fresh red cells, increased protein in the lumbar tap and the history and findings of active convulsions suggest that this bleeding was recent. The most common cause of such bleeding is trauma, of which there was no history. It is possible that this bleeding might have occurred as a result of convulsions primarily due to the subdural hematoma, which was proved by tap.

Subdural hematomas are not uncommon in infancy. Trauma, not necessarily obvious at the time of delivery, may be responsible. The symptoms of increased pressure arise as the red cells in the hematoma disintegrate and hemoglobin and protein pass into the serum, producing a hypertonic fluid with subsequent increase in the size of the mass. The blood obtained from the tap clotted on standing. This suggests recent bleeding. Other causes for both sources of bleeding at this age are scurvy and hemorrhagic tendencies. There was no history of vitamin C intake, and I doubt whether eight weeks is sufficient to produce scorbutic symptoms. There was nothing in the blood picture to suggest purpura, leukemia or other blood dyscrasias. The prothrombin time was normal, but this was after vitamin K administration. We know that the patient had obstructive jaundice. With this disorder bleeding tendencies are not uncommon, and I believe that the subdural and subarachnoid hemorrhages were due to vitamin K deficiency secondary to obstructive jaundice.

Despite the delay in onset of jaundice and in the appearance of clay-colored stools, I believe this infant was suffering from congenital atresia of the bile ducts, subdural hematoma and subarachnoid hemorrhage secondary to liver damage.

There were some x-ray films that I should like to see.

DR STANLEY M. WYMAN: The liver seems a little large. The spleen cannot be traced accurately. I am not too impressed by the abnormal contour of the liver. The lung fields are clear, and the heart is not remarkable.

DR BURGIN: I supposed, when I read about the enlargement of the left lobe of the liver, that possibly one hepatic duct closed later than the other hepatic duct, which might account for the greater enlargement on one side of the liver than the other. But I am not sure that that is a good explanation.

DR ALLAN M. BUTLER: I think the history as given omits the fact that a blood culture was taken and found to be negative.

cine was supplied to the stricken country, in addition to 32 tons of medical supplies and equipment

The various activities of this organization make up a considerable list. The technical health assistance that had been given to fourteen devastated countries by UNRRA was assumed by WHO. Two hundred and twelve fellowships in public health were awarded to representatives of various governments for study outside their own countries. The WHO mission in China assumed emergency public-health work as well as the training of medical and technical personnel, in Greece a malaria-control problem that included the spraying or dusting with DDT of nearly 3500 malaria-ridden communities was inaugurated.

Ethiopia, whose technical experts were liquidated during the war with Italy, was assisted in developing basic programs of medical training and public-health administration, the Ethiopian Red Cross was revived and reorganized.

In addition a number of studies were made by committees of experts. The Committee for the Preparation of the Sixth Decennial Revision of the International Lists of Diseases and Causes of Death made improvements in the classification of vital statistics. The Expert Committee on Biological Standardization adopted international standards for vitamin E, heparin and penicillin, and other expert committees considered such subjects as malaria, tuberculosis and venereal disease, the unification of pharmacopeias, pilgrimages (such as the Mecca pilgrimage), quarantine, yellow fever, habit-forming drugs, and alcoholism.

Under the joint auspices of the Interim Commission and the Unitarian Service Committee a group of eight American and two Swiss physicians and surgeons visited Austria last summer on a teaching mission.

The World Health Organization will become a specialized agency of the United Nations when twenty-six States members of the UN have ratified its constitution. This has already been done by eighteen members. Within six months of final ratification the first World Health Assembly will convene, and the permanent machinery of the organization will be established.

## NOW I LAY ME —

THOSE who received their medical training in a previous decade and have not since engaged in the practice of modern surgery may find themselves a little aghast at encountering postoperative patients walking about their rooms still reeking of ether. It is, however, in the tradition of today. We know that it is all for the best and that by these modern methods thromboses are prevented and embolic disturbances avoided. We have been made aware of the fact that despite their sojourn in a world of violence, most people still die in bed.

Those who indulge in a more placid form of medical practice than surgery have also become aware of the risks entailed in permitting patients to take too solidly to their beds. Levine<sup>1</sup> called attention to a few of them as long ago as September, 1944, when he showed that with bed rest a shift of edema may occur from the dependent parts of the anatomy to the patient's back, that recumbency increases the total blood volume, and adds the risk of hypostatic pneumonia, that in old men urinary retention may develop after recumbency has been instituted. In other words, there are dangers attendant upon bed rest besides that of pulmonary embolism.

Too often the colloquial expression "he took to his bed" implies a grim finality — a failure to rise again from the horizontal position.

Asher<sup>2</sup> carries the point still farther, expressing our old, innocent, somewhat naïve attitude toward bed in a quotation from *Hymns Ancient and Modern*, No. 23, Verse 3, as follows:

Teach me to live that I may dread  
The grave as little as my bed

Perhaps this obsolete attitude toward recumbency was also represented by the famous bed of Ware, on which several scores of couples could lie in apparent comfort. Disraeli, we are told, when in doubt took to his bed — a plagiarism on Voltaire.

Dr. Asher lists the strain of an overaddiction to recumbency on the respiratory system, the blood vessels, the skin, the muscles and joints, the bones, the renal tract, the alimentary tract, the nervous system and the mind.

Look at a patient lying long in bed. What a pathetic picture he makes! The blood clotting in his veins, the lime draining from his bones, the scybala stacking up in his colon, the flesh rotting from his seat, the urine leaking from his distended bladder, and the spirit evaporating from his soul.

The picture is overdrawn, he admits. Bed has its uses even in sickness, although the cardiac patient is often better off in a chair and all patients need exercise as soon as they are able to take it. It is moderation that Dr. Asher urges and that he implies in his final poetic outburst:

Teach us to live that we may dread  
Unnecessary time in bed  
Get people up and we may save  
Our patients from an early grave.

### REFERENCES

1. Levine, S. A. Some harmful effects of recumbency in the treatment of heart disease. *J. A. M. A.* 126:90-94, 1944.
2. Asher, R. A. J. Dangers of going to bed. *Brit. M. J.* 2:967, 1947.

## MASSACHUSETTS MEDICAL SOCIETY

### TREASURER'S REPORT COVERING REFUND DISTRIBUTION

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to district societies for 1948:

The Council voted to distribute the sum of \$8000.00 to district societies. The total number of payments of annual dues received by the Treasurer by March 1 to be counted for the refund, was 4541. Therefore the refund to the district societies for each paid fellow is \$1.76.

The following table gives the number of payments as of March 1, and the refund to each district as of March 12:

DISTRICT	NUMBER REPORTED PAID	REFUND
Barnstable	39	\$68.65
Berkshire	122	214.72
Bristol North	58	102.68
Bristol South	183	322.84
Essex North	180	317.01
Essex South	252	444.02
Franklin	40	70.40
Hampden	287	505.68
Hampshire	61	107.36
Middlesex East	137	241.38
Middlesex North	125	220.36
Middlesex South	937	1,650.06
Norfolk	828	1,459.02
Norfolk South	148	260.69
Plymouth	135	238.03
Suffolk	549	967.01
Worcester	374	658.69
Worcester North	86	151.40
	4,541	\$8,000.00

In 1947 for comparison the total number of payments for the refund was 4527.

ELIOT HUBBARD, JR., M.D. Treasurer

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY 1948

DISEASE	RESUME		
	FEBRUARY 1948	FEBRUARY 1947	SEVEN YEAR MEDIAN
Chancroid	4	2	1*
Chicken pox	1,839	2,542	1,340
Diphtheria	20	57	14
Dog bite	614	364	511
Dysentery bacillary	11	13	9
German measles	78	101	188
Gonorrhea	187	346	345
Gravid amniotitis	0	1	0*
Lymphogranuloma venereum	3	2	1*
Malaria	3	8	8
Mumps	2,092	2,021	1,877
Meningitis meningococcal	11	7	19
Meningitis Pfeiffer-bacillus	1	5	2
Meningitis pneumococcal	2	6	5†
Meningitis staphylococcal	0	1	0†
Meningitis streptococcal	0	0	0†
Meningitis, other forms	2	1	0†
Meningitis, undetermined	3	6	5†
Mumps	1,559	668	1,091
Pneumonia, lobar	134	178	323
Poliomyelitis	1	0	0
Salmonellosis	5	4	4
Scarlet fever	433	627	1,201
Syphilis	198	271	363
Tuberculosis pulmonary	218	189	197
Tuberculosis, other forms	11	13	14
Typhoid fever	5	0	2
Undulant fever	5	4	1
Whooping cough	294	620	620

\*Four year median.

†Six year median.

### COMMENT

Chicken pox, diphtheria, bacillary dysentery, measles, mumps, poliomyelitis and undulant fever are above the seven year median for these diseases.

German measles, lobar pneumonia, scarlet fever and whooping cough are below the seven year median.

Chicken pox is at the third highest prevalence for the month; the total cases having exceeded only in 1944 and 1947.

Mumps is epidemic in Greater Metropolitan Boston and the northeastern part of the State as far as the New Hampshire line.

For the second consecutive month scarlet fever is at low level since 1906.

Whooping cough is at the lowest prevalence since 1917.

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Belmont, Cambridge, 1; Everett 1; Revere 4; Somerville 2; Wayland 1; Winchester 3; total 20.

Dysentery bacillary was reported from 1 total 11.

Encephalitis infectiosa was reported from 1 total 1.

Malaria was reported from Malden, 1; total 3.

Meningitis meningococcal was reported from Fall River 1; Lexington 4; Malden, 1; total 6.

Meningitis Pfeiffer-bacillus was reported from 1 total 1.

Meningitis pneumococcal was reported from Weston 1 total 2.

Meningitis other forms was reported from Quincy 1 total 2.

Meningitis, undetermined, was reported from 1 North Attleboro 1; total 2.

Poliomyelitis was reported from 1 total 2.

Salmonellosis was reported from Malden 1; Melrose 1; total 2.

Septic sore throat was reported from 1 Falmouth 1; total 2.

Typhoid fever was reported from 1 total 1.

Undulant fever was reported from 1 Gloucester 1; total 1.

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## CORRESPONDENCE

### BLOOD GROUPING FACILITIES IN JEOPARDY

*To the Editor* The following letter from Commissioner Vlado A. Getting discloses a situation that is distressing to many of us who appreciate the importance of the laboratory services offered by the Massachusetts Department of Public Health. It will be even more distressing when physicians and patients throughout the Commonwealth realize that this important assistance can no longer be obtained.

When the Executive Committee of the Blood Grouping Laboratory appropriated the money, two years in succession, to enable the state laboratory to perform Rh testing and blood grouping on blood samples submitted by physicians, particularly in prenatal cases, it was our desire to explore the usefulness of such testing as a public-health measure and to find out how many doctors would avail themselves of this free testing for the benefit of their patients. Scientifically, there can be no question that Rh typing and blood grouping are important, not only to the general public but more particularly to women during gestation. By knowing the blood group and Rh type, the physician can protect his patient against the hazards of emergency need for transfusion, which occurs suddenly as a complication of pregnancy from time to time, and can protect the infant, in certain cases, by helping establish promptly the diagnosis of erythroblastosis fetalis in the newborn and by providing immediate treatment. That this service by the state laboratory has been most useful is proved by the large number of doctors who have availed themselves of it, and by the fact that more than 1000 cases per month are now being tested. Certainly the peak has not been reached, and eventually it is quite possible that five or six times the present number of specimens would be sent to the State Laboratory if this work were permitted to continue. Unfortunately, the Blood Grouping Laboratory cannot continue to support from its research funds what is essentially a routine procedure, no matter how important this is as a public-health measure. It seems a pity, therefore, that this work should be allowed to lapse merely because its great value is not recognized by a committee of laymen.

I trust that this correspondence will help bring a distressing situation to the attention of physicians of the Commonwealth who recognize the need for this protective laboratory work, and that these physicians and their patients who have benefited will call the attention of their legislators to the error that will be made if the services of the state laboratory are curtailed in this respect.

Dr. Louis K. Diamond  
Blood Grouping Laboratory  
Children's Hospital  
300 Longwood Avenue  
Boston, Massachusetts

Dear Dr. Diamond:

I am writing to inquire about the possibility of the continuation of a grant from your organization to provide Rh typing and blood grouping of bloods from pregnant women.

As you know, last year and this, the Department requested funds to carry on this service in its budget. The funds were not provided for the current year, and the item was not included in the Governor's budget, which was presented to the Legislature in January.

I had an opportunity to present this matter once more to the Ways and Means Committee a few days ago. I shall not know until the budget is passed whether further consideration will be given to this request, but because of the extraordinary demands being made upon the Legislature this year, it is altogether likely that the funds needed for this work will not be provided.

As you know, we were able to carry out over 9000 tests on pregnant women for physicians of the Commonwealth during the last twelve months. It will be quite a blow to the Department if it becomes necessary to curtail this service.

We are in essentially the same situation in diagnostic tests for virus diseases, which have been carried out in co-operation with the Virus Laboratory of the Harvard Medical School. Sufficient funds for the continuation of this work were not included in the expense item of the Division of Communicable Diseases in the budget submitted to the Legislature.

May I please hear from you regarding the possibility of continuing this service under a grant from your organization?

VLADO A. GETTING  
Commissioner

Commonwealth of Massachusetts  
Department of Public Health  
State House  
Boston

LOUIS K. DIAMOND, MD  
Director

Blood Grouping Laboratory  
300 Longwood Avenue  
Boston

### FURTHER COMMENT ON "UNNECESSARY OPERATIONS"

*To the Editor* I wish to subscribe to the comments made in the editorial "Unnecessary Operations," which appeared in the March 4 issue of the *Journal*. I imagine this editorial was written by one of your associates who is extremely well versed and qualified to comment on this subject. I simply wish to agree with statements and to add a comment or two based on my own experience.

The statistical improvement in mortality rates from appendicitis is most gratifying to everyone. The reasons for this improvement are, in my opinion, the result of better management of the individual patient and to a lesser extent better operative technique, and antibiotics and chemotherapy. It is not attributable to earlier or more accurate diagnoses so far as my observations indicate. Admissions to a specialized hospital for the young seem very much the same as they did fifteen years ago so far as appendiceal peritonitis is concerned. There has been an opportunity to observe admissions to two suburban and one Government hospital where the same situation obtains. My own experience in the past two years is similar.

I believe, therefore, that the article that inspired the editorial is capable of doing a great deal of harm. Relatively speaking, appendicitis is not a rare disease in childhood.

Prompt recognition of the disease is not common. Appendicitis is a diagnosis to be considered seriously when abdominal pain is a presenting symptom, and presence of localized tenderness, with or without supporting findings, is of the greatest importance. Home observation of such

patients is often unsatisfactory owing to environmental conditions including the emotional status of the family. Frequently, observations and laboratory support may not be feasible in the home. The proper place for a patient with an abdominal pain and without a definite diagnosis is in a hospital that is properly equipped and staffed.

HENRY W. HILDON, JR. M.D.

1101 Beacon Street  
Brookline

### NO MORE SPECIALISTS NEEDED

To the Editor: In the editorial entitled "The Second Age of Dependency" which appeared in the March 4 issue of the *Journal*, the last paragraph reads: "Perhaps we may need to add yet another specialty that will determine degrees of health rather than of disease whose representatives will endeavor to preserve, extend and enhance the physical and mental well being of the healthy and labor to keep apart the fields of the pediatrician and the geriatricist."

This sentence brings up a rather important point which needs certain clarification. The point is that a new, separate field of specialization may be needed. The clarification is that such a field properly should exist so far as the research aspect is concerned but it should not exist so far as the aspects of teaching or clinical practice are concerned. This is neither an argument simply of the old familiar general practitioner vs. specialist variety nor is it one of semantics.

The opinion of the slowly growing but still small number of physicians who have been interested in this field for many years (of whom I happen to be one) is somewhat as follows. The fundamental approach to a student's study of medicine should be through a study of man as a whole not through unrelated study of his various anatomic, physiologic and psychologic parts. Secondly the anthropologic, sociologic and general environmental aspects of man's existence should be given more consideration in the teaching given by medical school staffs. Thirdly the concept that an adequate understanding of man can be obtained through a consideration only of his symptoms or his disease is basically fallacious and should be replaced by a primary approach to man through consideration of him in his healthy state; the secondary approach being through disease. Finally these suggested changes in the fundamental approach to the study of medicine should become inherent in the approach of all teachers whatever specialty they may represent and should not become the province of a newly created group of specialists.

JOHN P. MORRIS, M.D.

Harvard University  
Department of Hygiene

### BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Studies from the Rockefeller Institute for Medical Research*. Reprints. Volume 133. 8<sup>o</sup> paper. 604 pp. New York: The Rockefeller Institute for Medical Research. 1947. \$2.00.

This volume is made up of reprints of papers originally printed in various periodicals and here brought together for convenience in reference. They constitute the results of investigations conducted at the Rockefeller Institute and published in 1946.

*A Handbook of Ocular Therapeutics*. By the late Sanford R. Gifford, M.D., professor of ophthalmology, Northwestern University Medical School, Chicago. Revised by Derreck Vail, M.D., D.O. (Oxon), professor of ophthalmology, Northwestern University Medical School, Chicago. Fourth edition. 8<sup>o</sup> cloth, 336 pp. with 66 illustrations. Philadelphia: Lea and Febiger. 1947. \$5.00.

Dr. Gifford died in 1944 and Dr. Vail assumed the task of revising this fourth edition of a standard textbook. There has been some revision to bring the text up to date. New material has been added on penicillin and the sulfonamides. The chapter on disorders of the muscular apparatus has been

eliminated since it was considered out of place in a book of this type. Selected references are appended to each chapter and there is a good index. The book is well published in every way. Although it has passed through four editions there is nothing to indicate its publication history. This is to be deplored for a book worthy of repeated editions should at least give the dates of the various editions on the back of the title page. The work is recommended for all medical libraries and should prove of value to specialists in the field of ophthalmology.

*Internal Medicine in General Practice*. By Robert P. McCombs, M.D., assistant professor of medicine and director of postgraduate teaching, Tufts College Medical School and senior attending physician, Joseph H. Pratt Diagnostic Hospital, Boston. Second edition. 8<sup>o</sup> cloth. 741 pp., with 122 illustrations. Philadelphia: W. B. Saunders Company. 1947. \$3.00.

Dr. McCombs has thoroughly revised this new edition of his work first published in 1943 and has adhered to his original plan of providing a text in which basic principles of everyday problems in internal medicine are factually reviewed and controversial material omitted or strictly condensed. Special emphasis has been placed upon diseases in which errors in diagnosis and therapy commonly occur. Diagnostic and therapeutic methods most readily adaptable for use in general practice have been stressed. New chapters have been added on psychiatric disorders and on the common vascular disorders of the extremities. Chemotherapy has been completely rewritten to include the use and abuse of penicillin and streptomycin and their relation to the sulphonamides. New material includes lumbosacral sympathetomy in hypertension, the rice diet in hypertension and certain kidney diseases, high protein diets and protein hydrolyzates in malnutrition, folic acid in macrocytic anemias and sprue, serum albumin in circulatory failure and nephrotic conditions, gamma globulins in measles and infectious hepatitis, chloroquine in malaria, para-aminobenzoic acid in neketical diseases, thiouracil in hyperthyroidism, estrogen therapy and castration in cancer of the prostate, benadryl and pyrimethamine in allergic disorders, cytochrome C in anoxic states, indione in psychomotor disorders and heparin and dicumarol in vascular emergencies. A list of selected references is appended to each chapter and there is a good index. The book is well published in every way and should be in all medical libraries and should prove valuable to practicing physicians.

*An Introduction to Biochemistry*. By William R. Fearon, M.A., Sc.D., M.B., fellow of Trinity College and professor of biochemistry, University of Dublin; fellow of the Royal Institute of Chemistry and member of the Royal Irish Academy. Third edition. 8<sup>o</sup> cloth. 569 pp. Illustrated. New York: Grune and Stratton. 1947. \$6.00.

This third edition of a work first published in 1934 has been thoroughly revised and many new sections added. More emphasis has been placed on certain subjects of special interest in clinical medicine, including acid base balance, animal calorimetry, carbon dioxide transport, energy transformation, blood chemistry, bone formation, food absorption and detoxication. A chapter on tissue chemistry has been added and the chapter on nutrients has been rewritten. A good index completes the volume.

*Surgery of the Ambulatory Patient*. By L. Kreeger Ferguson, M.D., professor of surgery, Graduate School of the University of Pennsylvania; professor of surgery, Woman's Medical College of Pennsylvania; surgeon, Graduate Hospital of the University of Pennsylvania; Woman's Medical College Hospital, Philadelphia; General Hospital and Doctors Hospital and consulting surgeon, United States Naval Hospital. With a section on fractures by Louis Kaplan, M.D., associate in surgery, University of Pennsylvania; chief Surgical Service, Mt. Sinai Hospital, and in charge of the fracture division of the Surgical Out Patient department, Hospital of the University of Pennsylvania. Second edition. 8<sup>o</sup> cloth. 932 pp. with 645 illustrations. Philadelphia: J. B. Lippincott Company. 1947. \$10.00.

Dr. Ferguson, in revising his standard office surgery first published in 1942, has endeavored to bring up to date subjects in which definite progress has been made since the pub-

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## CORRESPONDENCE

## BLOOD GROUPING FACILITIES IN JEOPARDY

*To the Editor* The following letter from Commissioner Vlado A. Getting discloses a situation that is distressing to many of us who appreciate the importance of the laboratory services offered by the Massachusetts Department of Public Health. It will be even more distressing when physicians and patients throughout the Commonwealth realize that this important assistance can no longer be obtained.

When the Executive Committee of the Blood Grouping Laboratory appropriated the money, two years in succession, to enable the state laboratory to perform Rh testing and blood grouping on blood samples submitted by physicians, particularly in prenatal cases, it was our desire to explore the usefulness of such testing as a public-health measure and to find out how many doctors would avail themselves of this free testing for the benefit of their patients. Scientifically, there can be no question that Rh typing and blood grouping are important, not only to the general public but more particularly to women during gestation. By knowing the blood group and Rh type, the physician can protect his patient against the hazards of emergency need for transfusion, which occurs suddenly as a complication of pregnancy from time to time, and can protect the infant, in certain cases, by helping establish promptly the diagnosis of erythroblastosis fetalis in the newborn and by providing immediate treatment. That this service by the state laboratory has been most useful is proved by the large number of doctors who have availed themselves of it, and by the fact that more than 1000 cases per month are now being tested. Certainly the peak has not been reached, and eventually it is quite possible that five or six times the present number of specimens would be sent to the State Laboratory if this work were permitted to continue. Unfortunately, the Blood Grouping Laboratory cannot continue to support from its research funds what is essentially a routine procedure, no matter how important this is as a public-health measure. It seems a pity, therefore, that this work should be allowed to lapse merely because its great value is not recognized by a committee of laymen.

I trust that this correspondence will help bring a distressing situation to the attention of physicians of the Commonwealth who recognize the need for this protective laboratory work, and that these physicians and their patients who have benefited will call the attention of their legislators to the error that will be made if the services of the state laboratory are curtailed in this respect.

Dr. Louis K. Diamond  
Blood Grouping Laboratory  
Children's Hospital  
300 Longwood Avenue  
Boston, Massachusetts

Dear Dr. Diamond

I am writing to inquire about the possibility of the continuation of a grant from your organization to provide Rh typing and blood grouping of bloods from pregnant women.

As you know, last year and this, the Department requested funds to carry on this service in its budget. The funds were not provided for the current year, and the item was not included in the Governor's budget, which was presented to the Legislature in January.

I had an opportunity to present this matter once more to the Ways and Means Committee a few days ago. I shall not know until the budget is passed whether further consideration will be given to this request, but because of the extraordinary demands being made upon the Legislature this year, it is altogether likely that the funds needed for this work will not be provided.

As you know, we were able to carry out over 9000 tests on pregnant women for physicians of the Commonwealth during the last twelve months. It will be quite a blow to the Department if it becomes necessary to curtail this service.

We are in essentially the same situation in diagnostic tests for virus diseases, which have been earned out in co-operation with the Virus Laboratory of the Harvard Medical School. Sufficient funds for the continuation of this work were not included in the expense item of the Division of Communicable Diseases in the budget submitted to the Legislature.

May I please hear from you regarding the possibility of continuing this service under a grant from your organization?

VLAO A. GETTING  
Commissioner

Commonwealth of Massachusetts  
Department of Public Health  
State House  
Boston

LOUIS K. DIAMOND, MD  
Director

Blood Grouping Laboratory  
300 Longwood Avenue  
Boston

FURTHER COMMENT ON  
"UNNECESSARY OPERATIONS"

*To the Editor* I wish to subscribe to the comments made in the editorial "Unnecessary Operations," which appeared in the March 4 issue of the *Journal*. I imagine this editorial was written by one of your associates who is extremely well versed and qualified to comment on this subject. I simply wish to agree with statements and to add a comment or two based on my own experience.

The statistical improvement in mortality rates from appendicitis is most gratifying to everyone. The reasons for this improvement are, in my opinion, the result of better management of the individual patient and to a lesser extent better operative technique, and antibiotics and chemotherapy. It is not attributable to earlier or more accurate diagnosis so far as my observations indicate. Admissions to a specialized hospital for the young seem very much the same as they did fifteen years ago so far as appendiceal peritonitis is concerned. There has been an opportunity to observe admissions to two suburban and one Government hospital where the same situation obtains. My own experience in the past two years is similar.

I believe, therefore, that the article that inspired the editorial is capable of doing a great deal of harm. Relatively speaking, appendicitis is not a rare disease in childhood.

Prompt recognition of the disease is not common. Appendicitis is a diagnosis to be considered seriously when abdominal pain is a presenting symptom, and presence of localized tenderness, with or without supporting findings, is of the greatest importance. Home observation of such

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Dr George P Sanborn, 384 Commonwealth Avenue, Boston announces his retirement from the practice of medicine on February 20 1948 His address will be Winterport, Maine

Dr Leslie H Van Raalte announces the removal of his office to 68 Russell Park, Quincy

TUFTS MEDICAL ALUMNI ASSOCIATION  
ANNUAL DINNER

The annual dinner meeting of Tufts Medical Alumni Association will be held at the Hotel Somerset Boston on Wednesday evening, April 7, at 6:30

The guest speaker will be Admiral Luis de Florez Sc.D. who will talk on 'New Engineering Developments in the Science of Medicine.'

Other speakers include Dr Stanley H Osborn commissioner of health Connecticut and professor of public health Yale University Reverend Michael J. Abern, S.J. director of seismology, Weston College Dr Frank R. Ober president Tufts Medical Alumni Association and Dr Bernard Appel professor of dermatology Tufts College Medical School Dr Leonard Carmichael president of Tufts College will discuss the progress of the medical school

MASSACHUSETTS GENERAL HOSPITAL  
RESEARCH COUNCIL MEETING

A meeting of the Massachusetts General Hospital Research Council will be held in the Bigelow Amphitheater of the White Building Massachusetts General Hospital on Thursday April 8, at 4:30 p.m.

## PROGRAM

Electrical Stimulation of the Orbital Surface of the Frontal Lobe and Frontal Lobotomy in Men Their effect on blood pressure and respiration Drs W. P. Chapman R. B. Livingston and K. Livingston

Clinical and Laboratory Studies on Beryllium Toxicology Drs R. S. Greer P. Nash and D. G. Freeman

## HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D Harvard Medical School on Tuesday April 13 at 8:00 p.m.

## PROGRAM

The Uptake of Radioactive Phosphorus by Gastric Carcinoma

Drs J. Schulman Jr. S. J. Gray and M. Falkenheim

Relief of Anginal Pain by Carotid Sinus Stimulation

Drs W. P. Harvey and S. A. Levine

The Pulmonary Capillary Pressure in Man

Drs H. K. Welles F. W. Haynes J. F. Gowder and L. Dexter

Circulatory Dynamics in Pulmonary Vascular Disease

Drs J. W. Dow, J. I. Whittenberger, E. C. Fpinger and H. P. Bran

The Use of Adrenocorticotrophic Hormone in the Evaluation of Adrenal Cortical Reserve in Man

Drs P. H. Forsham G. W. Thorn L. Recant and A. C. Hills

The Mechanism Involved in the Breakdown of Circulating Leukocytes

Drs P. Fremont Smith and C. B. Favours

Iron Transport

Drs C. E. Rath Jr. C. A. Finch J. C. Gibson 2nd and R. Fluharty

NEW ENGLAND SOCIETY OF  
ANESTHESIOLOGISTS

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Studies on mechanism

Drs Frank Pettigrew and J. W. Stutzman

Respiratory Arrest Resulting From Hypoxia after Diethylamine

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Effect of Pentothal Sodium on Blood Gas Transport.

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Physicians and medical students are invited to attend

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These meetings are open only to members and invited guests

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A meeting of the American Surgical Association will be held at the Chateau Frontenac, Quebec on May 27-28 and 29

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In response to popular request the program this year will again for the most part consist of symposiums and there will be one panel discussion

The program for the first three days at the Hotel Pennsylvania will consist of symposiums on gastroduodenal ulcer, ulcerative colitis, jaundice and metabolism, nutrition and allergy. The panel discussion which will be followed by a question and answer period will cover the topics of diabetic, tuberculous, psychosomatic and cardiac manifestations in gastrointestinal diseases

The fourth day of the session will be devoted to clinics at co-operating hospitals in New York City

Further details and a copy of the program may be obtained by application in writing to the Secretary, National Gastroenterological Association, 1819 Broadway, New York 23, New York

## AMERICAN COLLEGE OF CHEST PHYSICIANS

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The fourteenth annual meeting of the American College of Chest Physicians will be held at the Congress Hotel Chicago from June 17 to 20

STUDENTS INTERNATIONAL CLINICAL  
CONGRESS

The International Union of Students and the British Medical Students Association invite a delegation of fifteen medical students from the United States of America to a Students International Clinical Congress of 200 delegates to be held in England from July 6 to 24. Lectures, seminars

Figure 5, which shows, not for all medication common to the range dosage in milligrams per day, that the daily dosage was very consistently, smaller for all the normal records. Figure 5 also shows an unexpected result that 40 patients with normal records had discontinued all anticonvulsive medicine by the time

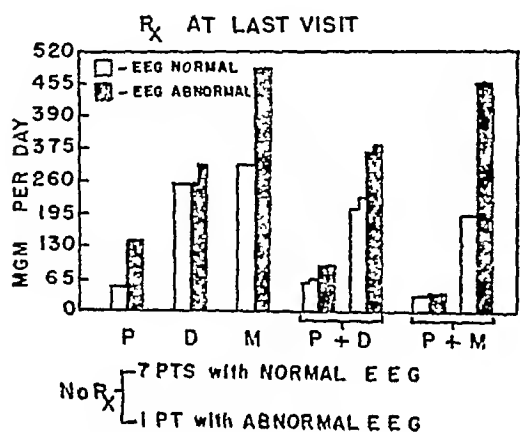


FIGURE 5 Medication in All Patients with Normal Electroencephalogram and in Selected Patients with Abnormal Tracings

The columns with notched tops represent patients given alternative dosages of medicine (such as one or two tablets of mebaral), the lower level of the notch representing the smallest and the higher level the largest average dosage determined by such alternatives. The various types of anticonvulsants prescribed are indicated as follows: P = phenobarbital, D = diphenylhydantoin sodium (dilantin), and M = mebaral.

of the last visit, whereas this was true for only 1 of the 38 selected abnormal group.

A detailed analysis was made of the case data on the 8 patients who, up to the last visit, had successfully discontinued anticonvulsive medication. This analysis suggests that the prognosis for remission of seizures off medicine is favorable under the following conditions: if the patient has had no attacks in infancy, if he shows, other than seizures, no evidence of encephalopathy, if he has been so mildly disturbed and is so well endowed as to have maintained a good social adjustment despite the seizures, if he presents, at the time that withdrawal of medicine is considered, a normal electroencephalogram (perhaps preferably done while the patient is off anticonvulsants for at least forty-eight hours), and if he has been seizure free for a period of one to two years, with anticonvulsants gradually reduced to, and maintained at, a minimal dosage of 1 capsule or tablet of phenobarbital, mebaral or dilantin daily or every other day for three months. The bias of this paper leads to a special emphasis on the normal record as a favorable criterion. A negative family history for epilepsy may also be prognostically

favorable. Probably, too, a relatively low maximal incidence of seizures—perhaps less than about twelve seizures a year at the worst period—is favorable. Apparently little prognostic significance attaches to the age at onset for the chronic adult epilepsy, as distinguished from attacks in infancy, the type of seizure or the relative incidence of seizures while the patient is awake and asleep. Finally, it may be added that remission of seizures off medicine is common in the late teens and early twenties.

Regarding the number of seizures while the patient is awake as compared with the number while he is asleep, whether at night in bed or during a daytime nap, one gets the clinical impression that the proportion of seizures while the patient is asleep is higher among patients with normal than among those with abnormal electroencephalograms. This impression appears to be confirmed by the analysis shown in Figure 6. In each group the clinical histories on 40 per cent of the patients failed to indicate any seizures in sleep. For the remaining 55 per cent of each of the two groups, Figure 6 shows a favorable trend toward a relatively higher incidence of seizures in sleep among patients having normal as compared with those having abnormal records.

These patients were also studied for four other features, which are described without graphic representation.

Thus, there was little contrast between the two groups regarding the occurrence of convulsions in

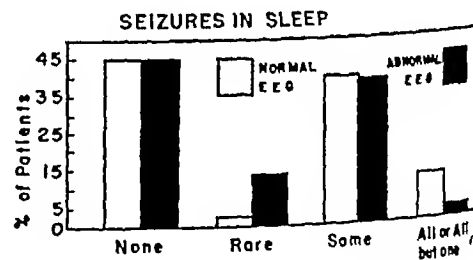


FIGURE 6 Occurrence of Seizures during Sleep

infancy—convulsions, that is, in the first five years of life and separated from the chronic adult epilepsy by a long, seizure-free period. Among the patients with normal records, there were 4, or 10 per cent, and among the selected abnormal group, there were 5, or 13 per cent, who gave a history of such infantile convulsions.

There was also little contrast between the two groups in the occurrence of post-traumatic or other encephalopathies, as distinguished from mere electrocortical abnormality. By implication or direct evidence, such encephalopathies were present in 15, or 33 per cent, of the 40 patients with normal and in 14, or 37 per cent, of the 38 selected patients with abnormal electroencephalograms.

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ther information may be obtained  
man, Committee on International  
Boston University School of  
Street, Boston

#### RESEARCH COUNCIL GRANTS FOR RESEARCH

The Committee on Human Reproduction of the National Research Council, acting for the National Committee on Maternal Health, Inc., announces that grants for research in the field of reproduction are available. Applications to become effective July 1, 1948, will be received until May 1, 1948, applications to become effective October 1, 1948, will be received until August 1, 1948.

The committee will consider support of biologic, clinical, economic, medical, psychologic and sociologic research dealing broadly with the field of human reproduction in general and with specific problems, including maternal and fetal physiology, the factors controlling conception, the physiology of fertilization and conception, and sterility. For the year 1948-1949, the committee will place specific emphasis upon investigations of the factors controlling conception, fertility and sterility, but other fields of endeavor will be supported if projects of special significance are presented. In subsequent years, changing emphasis may be anticipated.

The National Committee on Maternal Health has advised the National Research Council that it proposes to solicit funds to finance the program of research recommended by the Committee on Human Reproduction to an amount of approximately \$200,000 for 1948-1949.

Communications regarding grants should be addressed to Committee on Human Reproduction, National Research Council, 2101 Constitution Avenue, N W, Washington 25, D C

#### AMERICAN DERMATOLOGICAL ASSOCIATION

The annual meeting of the American Dermatological Association will be held in Coronado, California, from April 26 to 29 (secretary, Harry R. Foster, M D, 208 East Wisconsin Avenue, Milwaukee, Wisconsin)

#### AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

The annual meeting of the American Gastro-Enterological Association will be held in Atlantic City on April 30 and May 1 (secretary, Dwight L. Wilbur, M D, 655 Sutter Street, San Francisco, California)

#### AMERICAN SOCIETY FOR CLINICAL INVESTIGATION

The annual meeting of the American Society for Clinical Investigation will be held in Atlantic City on May 3 (secretary, E. A. Stead, Jr., M D, Duke Hospital, Durham, North Carolina)

#### ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The annual meeting of the Association of Military Surgeons of the United States will be held in Atlantic City, New Jersey, on May 4 and 5 (secretary, James M. Phalen, M D, Army Medical Museum, Washington 25, D C)

#### MEDICAL ASSOCIATION OF GEORGIA

The annual meeting of the Medical Association of Georgia will be held in Atlanta from April 27 to 30 (secretary, E. D. Shanks, M D, 478 Peachtree Street, N E, Atlanta 3, Georgia)

#### IOWA STATE MEDICAL SOCIETY

The annual meeting of the Iowa State Medical Society will be held in Des Moines from April 19 to 21 (secretary, John C. Parsons, M D, 406 Sixth Avenue, Des Moines 9, Iowa)

#### MEDICAL AND CHIRURGICAL FACULTY OF MARYLAND

The annual meeting of the Medical and Chirurgical Faculty of Maryland will be held in Baltimore on April 27 and 28 (secretary, George H. Yeager, M D, 1211 Cathedral Street, Baltimore 1, Maryland)

#### MEDICAL SOCIETY OF NEW JERSEY

The annual meeting of the Medical Society of New Jersey will be held in Atlantic City from April 26 to 29 (secretary, Earl L. Wood, M D, 315 West State Street, Trenton 8, New Jersey)

#### OKLAHOMA STATE MEDICAL ASSOCIATION

The annual meeting of the Oklahoma State Medical Association will be held in Oklahoma City from April 18 to 22 (secretary, R. H. Graham, 210 Plaza Court Building, Oklahoma City 3, Oklahoma)

#### STATE MEDICAL ASSOCIATION OF TEXAS

The annual meeting of the State Medical Association of Texas will be held in Houston from April 26 to 29 (secretary, Holman Taylor, M D, 1404 West El Paso Street, Ft. Worth 3, Texas)

#### SOCIETY MEETINGS AND CONFERENCES

##### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 1

###### FRIDAY, APRIL 2

\*10 00 a m - 12 00 m Medical Staff Rounds Peter Bent Brigham Hospital

###### MONDAY, APRIL 5

\*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital

###### TUESDAY, APRIL 6

\*12 00 m X-ray Conference Margaret Jewett Hall, Mt Auburn Hospital, Cambridge

\*12 15-1 15 p m Clinicoradiological Conference Peter Bent Brigham Hospital

\*1 30-2 30 p m Pediatric Rounds Burnham Memorial Hospital for Children, Massachusetts General Hospital

###### WEDNESDAY, APRIL 7

\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*2 00-3 00 p m Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater, Children's Hospital

6 30 p m Tufts Medical Alumni Association Annual Dinner Hotel Somerset Boston

\*Open to the medical profession

MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons American Industrial Hygiene Association American Conference of Governmental Industrial Hygienists American Association of Industrial Nurses Inc and American Association of Industrial Dentists. Hotel Statler Boston

MARCH 29 New England Heart Association Page 419 issue of March 18

MARCH 30-APRIL 1 American Association of Industrial Physicians and Surgeons Page 419 issue of March 18

APRIL 7 Tufts Medical Alumni Association Annual Dinner Page 455

APRIL 7-9 American Laryngological, Rhinological and Otolaryngological Society Page 419 issue of March 18

APRIL 7, 9, 14 and 16 American Trudeau Society Page 240, issue of February 12

APRIL 8 Endometriosis Dr John Fallon Pentucket Association of Physicians 8 30 p m Haverhill

APRIL 8 Massachusetts General Hospital Research Council Meeting Page 455

APRIL 10 American Congress of Physical Medicine Page 344 issue of March 4

(Notices concluded on page vii)

## NOTICES (Concluded from page 456)

- APRIL 12 Harvard School of Public Health Page 384 issue of March 11  
 APRIL 13 Harvard Medical Society Page 455  
 APRIL 13 New England Society of Anesthesiologists Page 455  
 APRIL 14 New England Dermatological Society Page 455  
 APRIL 19-21 American College of Physicians Page 211, is use of July 31  
 APRIL 20-29 American Dermatological Association Page 456  
 APRIL 29-MAY 2 American Academy of Pediatrics Page 240 issue of February 12  
 APRIL 30 and MAY 1 American Gastro-Enterological Association  
 MAY 3 American Society for Clinical Investigation Page 456  
 MAY 4 and 5 Association of Military Surgeons of the United States  
 MAY 6 Suffolk County Medical Society Page 344 issue of March 4  
 MAY 6-8 American Association for the Study of Gout Page 211 issue of July 31  
 MAY 12-14 American Association of Genito-Urinary Surgeons Sklyot Lodge Sklyot Pennsylvania  
 MAY 16-22 American Board of Obstetrics and Gynecology Inc Page 344 issue of March 4  
 MAY 16-23 International College of Surgeons Page 136 issue of January 21  
 MAY 17-20 American Urological Association Hotel Statler Boston  
 MAY 18-22 American Association on Mental Deficiency Copley Plaza Hotel, Boston  
 MAY 20-25 American Board of Ophthalmology Page 170, is use of January 29  
 MAY 25-27 Massachusetts Medical Society Annual Meeting Hotel Statler Boston  
 MAY 27-29 American Surgical Association Page 455  
 JUNE 7-10 National Gastroenterological Association Page 455  
 JUNE 17-20 American College of Chest Physicians Page 455  
 JUNE 21 and 22 American Society for the Study of Syphilis Page 384 issue of March 11  
 JUNE 28-30 American Academy of Pediatrics Hotel Schroeder Milwaukee Wisconsin  
 JULY 6-24 Students International Clinical Congress Page 455  
 JULY 12-17 First International Polymyxin Conference Page 16 issue of January 1  
 AUGUST 11-21 International Congress on Mental Health Page 344 issue of March 4  
 AUGUST 21-26 International Society of Hematology Page 419 issue of March 18  
 AUGUST 26-28 American Association of Blood Banks Page 420 issue of March 18  
 SEPTEMBER 13-15 American Academy of Pediatric Ophthalmology Hotel Seattle Washington  
 SEPTEMBER 20-23 American Hospital Association Page 110 issue of February 26  
 SEPTEMBER 29 All Indian Valley Medical Editors Association Page 170 issue of January 21  
 OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29  
 NOVEMBER 8-12 American Medical Health Association Page 420 issue of March 18  
 NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfont-Haddon Hall Hotel Atlantic City New Jersey

## DISTRICT MEDICAL SOCIETIES

## BOSTON SOUTH

APRIL 7 Addison Gilbert Hospital Gloucester University Trust  
 Dr George C. Frasier

## FRANKLIN

MAY 11 Annual Meeting Hotel Weld Greenfield

## MIDDLESEX EAST

MAY 12 Annual Meeting Bear Hill Golf Club Wakefield

## PLYMOUTH

APRIL 15 State Farm, Bridgewater  
 MAY 20 Lakewood Sanatorium Lakeside

## SUFFOLK

MAY 6. Censors Meeting

## WORCESTER

APRIL 14 Worcester Hahnemann Hospital  
 MAY 12. Annual Meeting

## TUFTS COLLEGE MEDICAL SCHOOL

## Postgraduate Division

and  
 BOSTON CITY HOSPITAL  
 Department of Orthopedic Surgery  
 FRACTURES

May 26 to May 29 1948 Inclusive

Dr Reginald Watson-Jones of London, England, will conduct the four-day full time course at the Boston City Hospital assisted by the leading surgeons of the Orthopedic Department. The subjects covered will be common fractures of the long bones of both extremities and of the spine, complicated and fracture dislocations of the common joint, principles of bone grafting and principles of internal fixation of fractures. Tuition fee \$20. Veterans may enroll under the Civil Bill of Rights. Apply to Miss Louise Murray, Secretary, Fifth Surgical Service, Boston City Hospital, 115 Harrison Avenue, Boston, Massachusetts, enclosing a check or money order payable to Trustees of Tufts College.

## Washingtonian Hospital

41-43 WALTHAM STREET BOSTON MASS

Incorporated 1859

Conditioned Reflex, Psychotherapy, Semi-Hospitalization  
 For Rehabilitation of Male Alcoholics

Treatment of Acute Intoxication and Alcohol Psychoses  
 Included

Outpatient Clinic and Social Service Department for  
 Male and Female Patients

JOSEPH THUMANN M.D. Medical Director

Visiting Psychiatric and Neurologic Staff  
 Consultants in Medicine, Surgery and the Other Specialties  
 Telephone MA 8-1780

## BREAST MILK

may be obtained at the offices and  
 laboratory of

The  
Directory for Mothers' Milk

Incorporated

221 Longwood Avenue, Boston  
 Telephone BE 2 5330

Prices will be adjusted to make the milk available  
 to all who need it

Sent packed in ice to all parts of New England

day

## PREGNANCY TEST

Complete reading in twenty  
 four hours, with a positive  
 result often obtained in eight  
 hours.

The Xenopus laevis test is well  
 established as a quick, accurate  
 and economical test for preg-  
 nancy.

New Eng J Med, 224:781, 1946  
 Correctly designed mailing cases  
 for all laboratory tests are  
 promptly furnished on request.  
 Results are telephoned to phy-  
 sicians anywhere in New Eng-  
 land, followed by a written  
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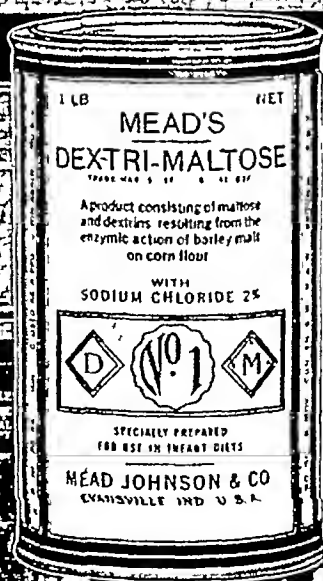
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# BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

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## SOME CLINICAL ASPECTS OF THE NORMAL ELECTROENCEPHALOGRAM IN EPILEPSY\*

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BOSTON

WHAT does it mean if the electroencephalogram of an epileptic patient is normal between seizures? On the one hand, the physician may have been led to believe that an abnormal electroencephalogram is highly characteristic of epilepsy. On the other hand, if he regularly refers his epileptic patients for electroencephalographic study, he forms the impression that, for a goodly portion of them, the tracings, at least at the time of examination, which is almost always done between seizures, are described as normal. This may be true even for patients examined when not taking anticonvulsive medicine.

Statistically, a review of the literature shows that the reported incidence of epileptic patients with normal electroencephalograms between seizures ranges from around 2 per cent to around 20 per cent. Historically, the smaller percentages seem to have been reported by the pioneer investigators. Thus Lennox, Gibbs and Gibbs,<sup>1</sup> in 1940, make incidental allusion to a series, perhaps not unselected, of 94 cases, in which the electroencephalograms were normal in only 2.2 per cent, whereas in a later study, published in 1941, Gibbs and Gibbs say that "in our experience less than five per cent of patients clearly diagnosed as epileptic have an initial record which is clearly normal." In 1941 Jasper and Kershman<sup>2</sup> reported a group of 494 patients with symptoms recognized clinically as epileptic, among whom only 26, or about 5 per cent, gave electroencephalograms in which "no obvious abnormality could be seen." In 1943 Solomon et al.<sup>3</sup> reported that, of 121 Navy recruits rejected with the diagnosis of epilepsy, 22 per cent had normal electroencephalograms. In 1944 Echlin<sup>4</sup> observed that the records were normal in 20 per cent of 100 epileptic patients. Hughes,<sup>5</sup> in 1944, reported that "a single electroencephalogram will give positive evidence of epilepsy in about 80 per cent of cases." In the same year Lambros, Case and Walker<sup>6</sup> stated

that, without hyperventilation, the records were abnormal in 75 per cent of patients with clinical evidence of epilepsy. Lennox,<sup>1</sup> in 1945, reported that in his series the electroencephalograms were normal in 18 per cent of patients with grand-mal seizures, 15 per cent with psychomotor seizures and 8 per cent with petit-mal seizures. In 1946 Baudoin, Fischgold and Remond<sup>7</sup> reported a 20 per cent incidence of normal records among epileptic patients examined between seizures. In our own series, discussed below, normal electroencephalograms were noted in 21 per cent of the patients examined between seizures.

So high an incidence of normal electroencephalograms among these patients makes obviously urgent an answer to the question asked at the beginning of this paper. The purpose of this communication is to report at least an initial, tentative and partial answer to that question.

This paper is based on the study of 193 patients attending the Epileptic Clinic of the Nerve Out-Patient Department at the Massachusetts General Hospital. Attendance at the clinic is restricted to patients ten to twelve years old or older. These patients were selected from the total attendance in accordance with only two criteria: the clinical diagnosis of epilepsy should be unequivocal, and for each patient at least one record should have been taken in accordance with a well standardized electroencephalographic procedure.

So far as technical details are concerned, electroencephalograms were recorded on a three-channel or six-channel Grass inkwriting oscillograph of the generally familiar type. In each case six or sixteen scalp electrodes were applied, in addition to two mastoid or ear-lobe electrodes, recordings were made from an extensive variety of scalp-to-scalp (so-called "bipolar") as well as of scalp-to-mastoid-or-ear-lobe (so-called "monopolar") linkages, at the end, the patient was hyperventilated for three minutes and observed for one minute after hyperventilation, and the whole recording was run for about thirty minutes. At the time of the test notes were made whether or not the patient was fasting and had been

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Figure 5, which shows, not for all medication common to the average dosage in milligrams per that the daily dosage was very consistently, smaller for all the normal records. Figure 5 also and unexpected result that of the 40 patients with normal records had discontinued all anticonvulsive medicine by the time

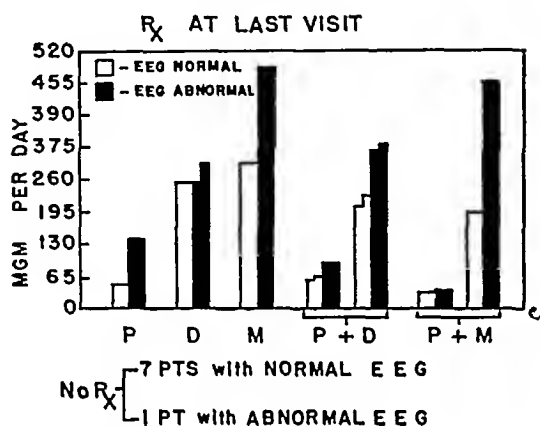


FIGURE 5 Medication in All Patients with Normal Electroencephalogram and in Selected Patients with Abnormal Tracings

The columns with notched tops represent patients given alternative dosages of medicine (such as one or two tablets of mebaral), the lower level of the notch representing the smallest and the higher level the largest average dosage determined by such alternatives. The various types of anticonvulsants prescribed are indicated as follows: P = phenobarbital, D = diphenylhydantoin sodium (dilatantin), and M = mebaral.

of the last visit, whereas this was true for only 1 of the 38 selected abnormal group.

A detailed analysis was made of the case data on the 8 patients who, up to the last visit, had successfully discontinued anticonvulsive medication. This analysis suggests that the prognosis for remission of seizures off medicine is favorable under the following conditions: if the patient has had no attacks in infancy, if he shows, other than seizures, no evidence of encephalopathy, if he has been so mildly disturbed and is so well endowed as to have maintained a good social adjustment despite the seizures, if he presents, at the time that withdrawal of medicine is considered, a normal electroencephalogram (perhaps preferably done while the patient is off anticonvulsants for at least forty-eight hours), and if he has been seizure free for a period of one to two years, with anticonvulsants gradually reduced to, and maintained at, a minimal dosage of 1 capsule or tablet of phenobarbital, mebaral or dilatantin daily or every other day for three months. The bias of this paper leads to a special emphasis on the normal record as a favorable criterion. A negative family history for epilepsy may also be prognostically

favorable. Probably, too, a relatively low maximal incidence of seizures—perhaps less than about twelve seizures a year at the worst period—is favorable. Apparently little prognostic significance attaches to the age at onset for the chronic adult epilepsy, as distinguished from attacks in infancy, the type of seizure or the relative incidence of seizures while the patient is awake and asleep. Finally, it may be added that remission of seizures off medicine is common in the late teens and early twenties.

Regarding the number of seizures while the patient is awake as compared with the number while he is asleep, whether at night in bed or during a daytime nap, one gets the clinical impression that the proportion of seizures while the patient is asleep is higher among patients with normal than among those with abnormal electroencephalograms. This impression appears to be confirmed by the analysis shown in Figure 6. In each group the clinical histories on 45 per cent of the patients failed to indicate any seizures in sleep. For the remaining 55 per cent in each of the two groups, Figure 6 shows a favorable trend toward a relatively higher incidence of seizures in sleep among patients having normal as compared with those having abnormal records.

These patients were also studied for four other features, which are described without graphic representation.

Thus, there was little contrast between the two groups regarding the occurrence of convulsions in

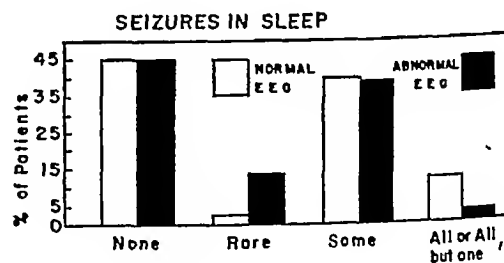


FIGURE 6 Occurrence of Seizures during Sleep

infancy—convulsions, that is, in the first five years of life and separated from the chronic adult epilepsy by a long, seizure-free period. Among the patients with normal records, there were 4, or 10 per cent, and among the selected abnormal group, there were 5, or 13 per cent, who gave a history of such infantile convulsions.

There was also little contrast between the two groups in the occurrence of post-traumatic or other encephalopathies, as distinguished from mere electrocortical abnormality. By implication or direct evidence, such encephalopathies were present in 13, or 33 per cent, of the 40 patients with normal and in 14, or 37 per cent, of the 38 selected patients with abnormal electroencephalograms.

Seven patients, or 18 per cent, with normal and 10, or 26 per cent, with abnormal records gave a positive family history of epilepsy.

In the three preceding comparisons, the differences were slight, but it may be significant that they were all in favor of the group with normal electroencephalograms.

Among the differences not represented graphically, however, a striking contrast between the two groups of patients appeared in the scholastic and occupational histories. Among those with normal records only 4, or 10 per cent, had been put out of school or had lost or changed jobs, or were unemployed because of their epilepsy, whereas 11, or 28 per cent, among the selected abnormal group had been put out of school or had lost jobs or were chronically unemployed or unemployable.

### DISCUSSION

From the observations cited above, it seems reasonable to conclude that a normal or almost normal electroencephalogram should be prognostically favorable and so of practical value, especially if it is recorded at the time of the first seizures when the future course of the illness is still unpredictable, whereas a grossly abnormal record should serve usefully to forewarn the physician of future difficulties and disappointments or to explain such difficulties and disappointments if they are already established.

### SUMMARY

Epileptic patients each showing at least one normal electroencephalogram between seizures and those showing only abnormal electroencephalograms between seizures are compared with reference to ten other aspects of the disease. All ten comparisons are favorable to the patients with normal records. In the patients with normal electroencephalograms there were later onset, fewer different kinds of spells, less frequent spells, greater response to medicine, more remissions while off medicine, more spells during sleep and greater ability to work, whereas patients with abnormal records had had spells in infancy, head injuries or other encephalopathies and positive family history of epilepsy.

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## SPONTANEOUS PNEUMOTHORAX\*

### A Clinical Study of One Hundred Consecutive Cases

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BOSTON

IT IS the purpose of this paper to present 100 consecutive, unselected cases of spontaneous pneumothorax in patients admitted to the Boston City Hospital in a nine-year period between 1934 and 1943. During the same period approximately 375,000 patients were admitted to the hospital, giving an incidence of 0.027 per cent, a figure that coincides with that of the series of Cohen and Kinsman.<sup>1</sup>

### DIAGNOSIS

The diagnosis in each case was made on the basis of the history, physical signs and x-ray findings. Positive x-ray findings were considered essential, and the diagnosis was not made in their absence.

The patients were divided into two groups, one consisting of 64 cases in which underlying pulmonary disease was known prior to entry or discovered during hospitalization, and the other com-

prising 36 cases of spontaneous pneumothorax occurring in apparently healthy persons. The older literature attributed a much higher percentage of spontaneous pneumothorax to underlying pulmonary lesions, especially tuberculosis. Of 918 cases collected by Biach,<sup>2</sup> 77.8 per cent were said to be due to tuberculosis. Morse<sup>3</sup> attributed 70 per cent of his 51 cases to tuberculosis, and Ayer<sup>4</sup> 69 per cent of his 72 cases, and West<sup>5</sup> found 99 of his 101 reported cases due to tuberculosis. However, the last series was derived from patients hospitalized for chronic lung diseases. As recently as 1931, Palmer and Taft<sup>6</sup> could find only 70 reported cases of spontaneous pneumothorax occurring in apparently healthy persons. Kjaergaard<sup>7</sup> focused attention on this condition with his monumental series in 1932.

### CLINICAL PICTURE

The history, symptoms and signs presented by the patients of both groups were essentially the same.

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Of both groups gave a history of prior to the acute episode. Of history of strenuous lifting, 4 of lifting, 3 of running upstairs, 2 of and 1 each of wrestling, playing pat, missing a step going down-an automobile. In the remaining 80 per cent the pneumothorax occurred during usual daily activities or at rest. In their series of 58 cases Ornstein and Lercher<sup>8</sup> found a history of exertion in 22 per cent.

Chest pain occurred in every patient and was always localized to the involved lung, with occa-

have been expected, there was a preponderance of cases in males except in the acute disorders, in which the ratio of males to females was about 1:1. The patients in this group ranged in age from twelve to eighty-two years, with an average age of forty-six years and one month. This is, in marked contrast to the patients in the second group, who had an average age of twenty-seven years and one month, with a range of three to fifty-three years.

The occurrence of a spontaneous pneumothorax in a patient above the age of forty-five should make one strongly suspicious of the presence of under-

TABLE 1 Incidence of Underlying Pulmonary Disorders in 64 Patients with Spontaneous Pneumothorax

DISEASE	TOTAL NO OF PATIENTS	MALE PATIENTS		FEMALE PATIENTS		AVERAGE AGE
		NO	PERCENTAGE	NO	PERCENTAGE	yr
Tuberculosis	38 ✓	29	76	9	24	44 0
Emphysema	5	4	80	1	20	59 6
Bronchietasis	5	4	80	1	20	43 0
Postpneumonic empyema	4	3	75	1	25	50 0
Bronchial asthma	3	3	100	0	0	36 0
Lung abscess	3	0	0	3	100	32 0
Metastatic carcinoma of lung	2	1	50	1	50	54 0
Pneumonia	2	1	50	1	50	80 0
Bronchogenic carcinoma	1	1	100	0	0	61 0
Pulmonary infarct	1	0	0	1	100	17 0
Totals	64	47		17		
Averages			73 4		26 6	46 1

sional radiation to the abdomen, neck or lower back. Dyspnea was also universally complained of, but frequently appeared to be more subjective than objective. Cough and fever were common in patients of the first group, but only 5 patients in the second complained of cough, and only 3 had an elevated temperature, which was slight. Hemoptysis occurred in 2 patients with underlying tuberculosis.

The physical signs varied with the degree of lung collapse. It was generally found that when the degree of pneumothorax was more than 40 per cent, classic signs could be elicited. These included hyperresonance, diminished or absent vocal and tactile fremitus, absent breath sounds, mediastinal shift and positive coin test. The physical signs may be scant or absent in the presence of small pneumothoraces. In the first group the additional findings of the underlying pulmonary lesion were also present. Right-sided and left-sided pneumothorax occurred with equal frequency in both groups. One patient with bilateral spontaneous pneumothorax had far advanced bilateral tuberculosis.

#### ASSOCIATED PULMONARY DISEASE

Table 1 shows the incidence of the various pulmonary disorders that were found associated with the patients in the first group. Tuberculosis constituted the underlying cause in 50 per cent of this group and in 38 per cent of the total. As might

lying pulmonary disease. The following case illustrates this point.

K. H. (B. C. H. 1129821), a 53-year-old man, was admitted to the hospital in May, 1943. He had been perfectly well until 2 hours prior to entry, when he noticed a sudden, sharp, right-sided pleuritic chest pain accompanied by dyspnea. Physical examination revealed classic signs of a right pneumothorax and was otherwise negative. Two x-ray films of the chest confirmed the presence of a 50 per cent pneumothorax on the right. An area of patchy density was described in the collapsed right upper lobe.

Examination of the blood revealed a red-cell count of 4,720,000, with a hemoglobin of 14 gm., and a white-cell count of 9000, with 79 per cent neutrophils, 18 per cent lymphocytes and 3 per cent monocytes. The blood sedimentation rate was 15 mm per hour. Two urinalyses were negative.

The patient left the hospital against advice on the 6th hospital day before further investigation could be carried out.

He was readmitted 14 months later with a 10-week history of cough, right-sided chest pain radiating down the right arm, progressive weakness, anorexia and a weight loss of 25 pounds. Physical examination revealed a Horner's syndrome on the right, signs of a mass in the right upper lung and a mediastinal shift to the left. A large tender mass was palpated in the right flank. Laboratory studies were negative except for a moderate degree of anemia.

The patient went downhill rapidly and died 3 weeks after admission. Autopsy revealed a renal-cell carcinoma of the right kidney, with metastases to the left adrenal gland and right lung.

In this case the spontaneous pneumothorax undoubtedly represented the lung metastasis, and since renal-cell carcinoma tends toward solitary metas-

tases, it is interesting to speculate whether early diagnosis might have prolonged the patient's life

### SPONTANEOUS PNEUMOTHORAX IN APPARENTLY HEALTHY PERSONS

Of the 36 cases in the second group 30, or 83.3 per cent, occurred in male patients. This predilection has been reported by all previous investigators. As stated above, there was an age range of three to fifty-three years, with an average age of twenty-seven years and one month. Table 2 shows the contrast of age incidence by decades between the two groups.

Of the 36 patients in the second group 21 were successfully followed for periods ranging from one and a half to twelve years. Of these, 2 had died of other causes. 1 of cirrhosis of the liver five years after the occurrence of the pneumothorax, and the other of acute yellow atrophy of the liver two and a half years after the original attack. Post-mortem examination of the lungs in the latter case was reported as negative.

Three patients had multiple recurrences — an incidence of 14.3 per cent (in other series a recurrence rate of 10 to 30 per cent has been reported<sup>4</sup>). One of these 3 patients had multiple attacks, estimated by the patient as numbering eighteen to twenty. Chest x-ray study was negative six and a half years after the original attack, and the patient was considered a candidate for the induction of a chemical pleuritis. One female patient had a total of seven recurrences and had a negative x-ray examination twelve years after the original attack. The third patient in this group had a total of seven recurrences. Between the fourth and fifth attacks he developed clinical and x-ray evidence of tuberculosis and he died three and a half years after the first occurrence of pneumothorax. After the first four episodes the lung fields had appeared clear after re-expansion, and during the first and second admissions tuberculin tests had been negative in dilutions of 1:100. This patient represents the only one in the second group who was known to have developed tuberculosis. Kjaergaard<sup>7</sup> followed 49 patients of this type and found only 1 who developed tuberculosis subsequent to spontaneous pneumothorax. In a review of the literature Perry<sup>8</sup> could find a record of only 6 cases developing tuberculosis after a benign spontaneous pneumothorax.

One patient had a typical attack of spontaneous mediastinal emphysema 3 years after the first occurrence of pneumothorax and was alive and well nine years later.

### TREATMENT

All patients were treated with bed rest and symptomatic medication to relieve pain and cough. Aspiration of air to relieve dyspnea was done in 3 cases. Whenever possible, appropriate therapy was directed toward the underlying condition in patients in the first group. Patients with tubercu-

losis were transferred to sanatoriums shortly after admission. Hospitalization of patients in the second group varied from two to thirty-six days, with an average stay of eleven days. There was no immediate mortality in this group. Four patients in the first group expired during the hospital stay.

### SUMMARY AND CONCLUSIONS

One hundred cases of spontaneous pneumothorax in patients admitted to the Boston City Hospital between 1934 and 1943 are presented. Of these,

TABLE 2 Comparison of Age Incidence of Spontaneous Pneumothorax in Patients with Underlying Pulmonary Disease and in Apparently Healthy Persons

AGE yr	PATIENTS WITH UNDERLYING PULMONARY DISEASE		APPARENTLY HEALTHY PERSONS	
	NO.	PERCENTAGE	NO.	PERCENTAGE
0-9	0	0	1	2.8
10-19	4	6.3	7	19.4
20-29	9	14.0	17	47.2
30-39	12	18.8	5	13.9
40-49	10	15.6	5	13.9
50-59	13	20.3	1	2.8
60-69	11	17.2	0	0
70-79	3	4.7	0	0
80-89	2	3.1	0	0
Totals	64		56	

64 patients, with an average age of forty-six years and one month, had underlying pulmonary disease, of which tuberculosis constituted 59 per cent.

Thirty-six cases occurred in apparently healthy persons with an average age of twenty-seven years and one month, 21 of whom were successfully followed for periods of one and a half to twelve years. Three patients, or 14.3 per cent, had recurrences. One had a subsequent attack of spontaneous mediastinal emphysema. Another developed tuberculosis after four recurrences.

A comparison of the history and clinical signs and symptoms in the two groups is presented.

The occurrence of a spontaneous pneumothorax in a person over forty-five years of age should excite suspicion of an underlying pulmonary lesion. A case is presented to illustrate this point.

The prognosis in the apparently healthy person with a spontaneous pneumothorax is excellent from the standpoint of both immediate recovery and the subsequent development of tuberculosis.

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## STREPTOMYCIN TREATMENT OF BACTERIAL ENDOCARDITIS\*

## Report of a Case

BENEDICT F MASSELL, M D,† J WALLACE ZELLER, M D,‡ JAMES W DOW, M D,\$ AND  
DONALD HARTING, M D ¶

With the Technical Assistance of Mary Meyeserian||

BOSTON

A CASE of bacterial endocarditis due to a gram-negative organism belonging to the genus *Hemophilus* is reported for two reasons: it is one of the early reported recoveries following treatment with streptomycin—perhaps the first patient of this kind to recover without any other therapy, and recovery followed a shorter course of treatment than would ordinarily be planned.

## CASE REPORT

S K, a 9-year-old girl, entered the House of the Good Samaritan on June 28, 1946, complaining of fever of about 3 months' duration. Her birth and early development were thought to have been normal. At 4 years of age she experienced an attack of fever accompanied by migratory joint pain. From that time on she was thought to tire easily, to be short of breath, and to become blue on climbing a flight of stairs. The physician who referred her to the hospital first saw her when she was 6 years old. He observed her to be cyanotic, to have an enlarged heart by physical examination and by fluoroscopy, and to have a hemoglobin of 13.5 gm. Despite these findings she remained in fair health for the next 2 years.

On April 27, 1946, the patient returned to the physician's office complaining of fever of an indefinite duration. Examination showed her to be intensely cyanotic, with a liver edge palpable 4 fingerbreadths below the costal margin and with an enlarged spleen. She was admitted to another hospital 2 days later. At that institution the hemoglobin was 12.7 gm, the red-cell count 4,300,000, and the white-cell count 14,200. The heart was enlarged by x-ray study. Three blood cultures grew no organism. For 1 month of hospitalization the course was febrile, with daily oral temperature elevations to 102°F. The physical findings did not change. From discharge on May 24 until her admission to the House of the Good Samaritan she remained in bed at home, where she continued to run a fever. On one or more occasions during this period there were minor hemoptyses.

Physical examination disclosed a thin, pale child, who was small for her age and moderately cyanotic. The weight was 50 pounds. There was minimal clubbing of the fingers and toes. The heart was large, with a forceful, apical impulse for a maximum of 7 cm from the midsternal line in the fourth intercostal space, 1.5 cm outside the midclavicular line. Dullness to percussion was detected well out in the second and third left interspaces. There was a Grade IV to Grade V, rough, systolic murmur and thrill maximum in the first and second left interspaces. The murmur was well transmitted to the apex, neck and interscapular region and tended to mask the basal but not the apical heart sounds. There was a loud, diastolic, third heart sound, but no diastolic murmur. Arterial and venous cervical pulsations were present with the patient erect. The blood pressure was 125/80, and femoral pulsations were strong. The liver edge was felt 4 cm below the costal

margin but was not tender. The spleen was easily palpable. No petechiae were seen, nor were Osler's nodes demonstrated.

Examination of the urinary sediment revealed 15 to 20 red cells per high-power field. The red-cell count was 4,960,000, with a hemoglobin of 11.8 gm, and the hematocrit was 40 per cent. The white-cell count was 11,600. The corrected sedimentation rate by the Ernestine-Rourke method was 1.5 mm per minute (normal, 0.05 to 0.40 mm per minute). Agglutinations for brucellosis and typhoid fever were negative. The electrocardiogram was typical of extreme right-sided heart strain. Fluoroscopy showed the heart to be large, with a massive right ventricle and dilated main pulmonary artery, but small intrapulmonary branches and an inconspicuous aortic knob.

From admission until specific treatment was begun on July 19 the patient ran a fever, the rectal temperatures spiking daily to 103°F at 4:00 p.m. and falling to 96°F each morning at 8:00 o'clock. The blood was cultured on June 28, on July 1 and 2 and again just before treatment was started.

TABLE 1 Serum Levels after Single Intramuscular Injections of 250,000 Units of Streptomycin

DATE	TIME OF WITHDRAWING BLOOD SAMPLE	INTERVAL SINCE PREVIOUS INJECTION hr	SERUM STREPTOMYCIN LEVEL units per cc
July 22	3:25 p.m.	3	20
	4:00 p.m.	3½	66
	4:30 p.m.	1	50
	5:30 p.m.	2	20
	6:30 p.m.	3	10
July 23	12 noon	3	20

on July 19. In all, fourteen flasks were inoculated, and in every one there grew out a small, gram-negative, coccobacillus.

This micro-organism was studied in some detail by George E. Foley, of the Children's Hospital, Boston, who found that it presented the morphologic, cultural and biochemical characteristics of the genus *Hemophilus*. It did not agglutinate with *Haemophilus influenzae* antisera, Types A through F. Its ability to grow in mediums without hematin (X factor) but not in those without yeast (V factor) was interpreted as being typical for *H. parainfluenzae*.<sup>1</sup>

Sensitivity of the organism to known concentrations of penicillin and streptomycin was determined on blood-agar plates rather than in dextrose broth, in which the organism grew very poorly. A control organism of known penicillin sensitivity (when tested in broth) was found to be inhibited with the expected concentration of penicillin on the blood-agar medium.

Growth of the organism was not inhibited by concentrations of penicillin as high as 10 units per cubic centimeter. Streptomycin inhibited growth in concentrations greater than 2 units and less than 4 units per cubic centimeter. These results indicated that *in vitro* the organism was resistant to penicillin but sensitive to concentrations of streptomycin easily obtainable in the blood. Table 1 shows that serum streptomycin concentrations from five to fifteen times that required to inhibit the organism *in vitro* were actually obtained during therapy.

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||Technician, House of the Good Samaritan.

On July 19 treatment was started with 2 gm. of streptomycin daily given in eight divided doses at 3 hour intervals by intramuscular injection. The course planned was to extend over a 14-day period, during which the patient was to receive a total of 28 gm. of the drug. The septic fever broke immediately after the first dose. Blood cultures taken 18 hours after the start of therapy those made while on treatment and those taken as late as 2 months after the end of therapy showed no growth (Fig 1).

The patient improved during the first 5 days of treatment until it became necessary to use a different brand of

infections are by members of the genus *Hemophilus*. Thayer<sup>2</sup> implicated this group in 29 per cent of all cases of infective endocarditis. As in bacterial endocarditis due to the *Streptococcus viridans*, infection is always implanted on a congenital defect or previously damaged cardiac valve, and the clinical manifestations, course and prognosis of the untreated disease are the same with either organism.<sup>2-5</sup>

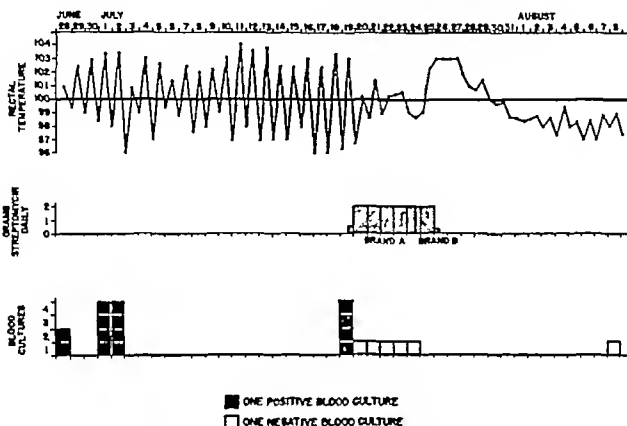


FIGURE 1 Temperature Streptomycin Dosage and Blood Cultures in a Case of Bacterial Endocarditis

streptomycin. The second lot caused fever with rectal temperatures sustained between 101 and 103 F and local irritation so severe that treatment had to be discontinued after a total of only 13.5 gm. had been given in 634 days. There was no other evidence of a toxic reaction to the drug.

After omission of therapy the temperature fell by lysis in 4 days. The patient improved steadily and uneventfully except for a small hemoptysis on July 28. She gained 13 pounds and seemed entirely well at time of discharge on November 24. Although the liver became smaller the spleen remained palpable throughout hospitalization.

During convalescence the red-cell count rose to 5 750 000, the hemoglobin to 16.3 gm. and the hematocrit to 54 per cent, although with the disappearance of the signs of heart failure cyanosis became minimal. These high values supported the possible diagnosis of an underlying cardiac anomaly consisting of a right-to-left shunt. Consequently the patient was referred to Dr. Lewis Dexter and his associates at the Peter Bent Brigham Hospital for study by venous catheterization. Dr. Dexter's findings were consistent with a high degree of pulmonary stenosis together with a small ventricular septal defect and probable overriding aorta. The Blalock operation was not advised by Dr. Dexter because the oxygen saturation of the peripheral arterial blood was found to be high (87 per cent).

The patient was well and active at the time of writing 1 year after the completion of therapy.

#### DISCUSSION

Gram-negative bacilli are only occasionally the agents causing bacterial endocarditis. Of the small proportion of endocarditides so caused most of the

Craven, Poston and Organ,<sup>3</sup> in 1940, were unable to find a report of a case due to an influenzal or parainfluenzal organism in which the patient recovered.

Since 1941 apparent cures have been reported in 8 patients treated with sulfonamides and antibiotics.<sup>4-6</sup> Of 2 cases treated at Mount Sinai Hospital, 1 was arrested with a sulfonamide alone, whereas the other responded to sulfapyridine and hyperthermia.<sup>4</sup> After each had proved ineffective alone, penicillin and sulfamerazine combined sterilized the blood of a patient reported by Priest and McGee.<sup>7</sup> Of 2 cases reported by Hunter and Duane,<sup>8</sup> 1 yielded to sulfadiazine after penicillin had failed. The second patient recovered after penicillin, sulfadiazine and streptomycin had been used.<sup>8</sup> Streptomycin may well have been the effective agent in this case, but unfortunately three blood cultures taken before streptomycin was started remained sterile.

More recently Hunter<sup>8</sup> added 2 cases from his own experience and 5 more supplied to him by Dr. Chester Keefer. In these 7 cases, 3 patients have survived. Each of the survivors received penicillin or a sulfonamide prior to or in conjunction with



streptomycin, although the latter was credited with the favorable outcome

A much wider experience is available in the treatment with streptomycin of influenzal and para-influenzal infections of other systems. The drug has proved to be effective in meningitis, pulmonary disease, bacteremia and urinary-tract infection<sup>10-12</sup>. Unfortunately, its usefulness has been limited by the rapid development of organism resistance when the concentration of the drug at the site of the lesion is inadequate and by the toxic effects that have lately become apparent.

Deliberate attempts to increase the resistance of gonococci to streptomycin in vitro have resulted in tolerance by the organism of from 1900 to perhaps as much as 75,000 times the originally effective concentration.<sup>13</sup> This demonstration has been paralleled clinically with *H. influenzae* infections, as well as with infections due to other organisms.<sup>14, 15</sup> In these cases loss of therapeutic effect has been associated with a decreased sensitivity of successively isolated organisms. In 1946 Keefer<sup>11</sup> considered it advisable to maintain at the lesion a concentration of streptomycin from four to eight times that required to inhibit the organism in vitro so that infection could be eradicated before resistance to the drug developed. No patient in Hunter's<sup>9</sup> group recovered if a concentration greater than 8 microgm of streptomycin per cubic centimeter was required to inhibit the causative organism in vitro.

The important toxic manifestation is severe and possibly permanent eighth-nerve damage, with not only vestibular dysfunction but also nerve deafness.<sup>16</sup> Damage increases with both the amounts of streptomycin given and the period of administration. Histamine-like reactions may be effectively treated with benadryl or pyribenzamine, and local irritation is not a problem with pure preparations.

It is apparent that high concentrations of streptomycin are desirable from the start, that if resistant strains appear, prolonged treatment may be useless, and that the longer the treatment, the greater the risk of vestibular damage and nerve deafness. If effective a short, intensive course should theoretically be ideal. Hunter recommends three or four weeks of treatment with 2 to 6 gm of streptomycin daily, with the reservation that if the case is clinically favorable and nerve deafness is developing the drug

may be stopped after two weeks. It is of interest that the patient in the case reported above recovered after only six and a half days of treatment.

### SUMMARY

Streptomycin was an effective agent for treatment in a case of endocarditis caused by a gram-negative organism belonging to the genus *Hemophilus*.

The causative organism was isolated and its sensitivity to the drug in vitro determined before treatment was started.

The concentration of streptomycin maintained in the blood was never less than twice and rose as high as fifteen times that required to inhibit the organism in vitro.

A short, intensive course of streptomycin eradicated the infection in this case.

We are indebted to George E. Foley and Commander L. A. Barnes, H (S), USNR, for their identification of the organism, and to Dr. Norman Pokorny, who diagnosed the disease and referred the patient for treatment.

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## MALARIA\*

## Observations on Treatment with Chloroquine (SN 7618) and Combined Quinine and Plasmochin

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NUMEROUS excellent descriptions of the clinical symptomatology, course and response to quinacrine (atahrine) therapy of relapsing vivax malaria of Pacific origin have appeared in the last four years. Most and his associates<sup>1</sup> have described the effects on the relapse rate of combined quinine and plasmochin treatment. Similar but less complete studies have been made by Bianco and his co-workers<sup>2</sup> and others. Loeh,<sup>3</sup> Most et al.<sup>4</sup> and Faust<sup>5</sup> have described the early results of treatment with chloroquine (SN 7618). All these studies were carried out in the various military services, with the patients usually hospitalized throughout the entire period of therapy and follow-up observation. It was believed, therefore, that a longer post-therapeutic follow-up period of patients who had been living under ordinary civilian conditions would prove of value, and that general trends in the course of the infection might be of interest to the practitioner.

## MATERIALS AND METHODS

During the year of July 1, 1946, to July 1, 1947, 125 patients with proved malaria due to *Plasmodium vivax*, all of Pacific origin, were admitted to the Veterans Administration Hospital, West Roxbury, Massachusetts. All had received suppressive quinacrine therapy while stationed in malarial zones, and most had been given various doses of quinacrine for prior clinical attacks. Once a positive smear had been obtained, either of two methods of treatment was offered. Those who desired as short a period of hospitalization as possible were treated with chloroquine diphosphate. The dosage was 1.0 gm. (4 tablets, each containing 0.25 gm. of the diphosphate) followed in eight hours by 0.5 gm. (2 tablets). A single dose of 0.5 gm. was administered on the second and third days of treatment. Most patients were discharged on that day, with instructions to take 0.5 gm. (2 tablets) every Sunday for five weeks. Out-patient follow-up physical examinations with smears for malarial parasites and an extensive symptomatic history were obtained every two months. If an unusual clinical finding such as a

positive serologic test had been noted, the checkups were made on a monthly basis.

Patients who complained of over five recurrent attacks of malaria and those who were able to spend two weeks in the hospital were placed on the combined quinine-plasmochin regime as outlined by Most et al.<sup>1</sup> Plasmochin naphthoate, in 0.02-gm doses, was administered every eight hours for fourteen days. Quinine sulfate was prescribed in 1.0-gm doses every eight hours for one day followed by 0.6 gm every eight hours for thirteen days. Repeated urinalyses, blood counts and electrocardiograms were performed to detect any evidence of toxic reactions to the drugs. The medications were given simultaneously. Fluids were forced during the acute relapse, ferrous sulfate was prescribed when any significant anemia was detected on admission, and the patients were restricted to no greater activity than a short walk to the dining hall or bathroom. Follow-up examination was identical to that described for patients treated with chloroquine.

## RESULTS

Eighty-nine patients were followed for a period of six to twelve months, and the remainder for one to six months. Striking differences between the results of the two treatments were noted and are discussed separately. Because a veteran may receive greater compensation if a greater relapse rate is indicated, the relapses were divided into proved or laboratory relapses and symptomatic relapses with negative smears.

Twenty-six patients received chloroquine therapy. Within three months 9 had experienced repeated symptoms of an acute relapse associated with a positive smear for *P. vivax*. One patient relapsed seven, and 1 nine months after completion of this course of therapy. Ten patients were subsequently treated with quinine and plasmochin. The eleventh, a physician, experienced repeated relapses every three to five months, with an increasing interval between relapses. An additional 11 patients complained of slight fever and other minor symptoms suggestive of relapse, but self-medication with quinacrine was taken and subsequent smears were negative. The total failure rate of 84 per cent and laboratory rate of 42 per cent were essentially the same as those obtained with quinacrine. No toxic symptoms from the use of chloroquine were noted. Its effect on the acute relapse was as prompt as that of quinacrine. It was more pleasant for the patient

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\*Furnished through the courtesy of Mr. Shepherd M. Criss, Department of Medical Research, Winthrop Chemical Company, Inc. It is pointed out that the doses employed in this study differed from those given in the earlier reports on this drug in which tablets containing 0.30 gm. of the base were administered. Only tablets containing 0.15 gm. of the base (0.25 gm. of the diphosphate) are now available.

to take, since it neither produced gastrointestinal irritation nor discolored the skin. No definite relapses occurred during the five-week period of suppressive therapy, although 2 patients stated that they felt sick every Saturday, just before taking the weekly suppressive dose.

Sixty-three patients treated with the combined quinine and plasmochin regime were followed for six to twelve months after completion of therapy. No case of a laboratory relapse occurred. Sixteen patients stated that they had experienced symptoms, which they interpreted as an attack of malaria—a symptomatic relapse rate of 26 per cent. One of these had persistent splenomegaly, 6 were sub-

sequently admitted to the hospital for "malarial attacks," and negative smears were obtained. In some cases adequate cause for the fever was found in infection of the urinary or respiratory tracts, and the remainder were afebrile. No laboratory relapses occurred in an additional 40 patients followed for less than six months. All patients stated that they noted great improvement in their sense of well-being.

The toxic manifestations of plasmochin were not serious or severe. The principal toxic symptoms or signs observed were mild to severe epigastric burning, abdominal cramps and diarrhea. These symptoms most commonly occurred during and after the fifth day of therapy. Abdominal pain was severe enough in 2 cases to necessitate discontinuance of the medication for several doses before the treatment could be continued to completion. There was no relation of the severity of the gastrointestinal symptoms to other manifestations of toxicity. X-ray

studies in several cases during this period of discomfort failed to reveal any gastric hyperperistalsis or intestinal spasm.

Circulatory signs and symptoms consisted of the appearance or disappearance of ventricular extrasystoles concurrently with the administration of the drug in 1 case. Cyanosis was rarely observed, as was the central-nervous-system symptom of "nervousness." No evidence of any hemolytic anemia was encountered.<sup>6</sup> It should be emphasized, however, that only white patients were treated and that they were kept on restricted activity.

The usual symptoms of quinine toxicity—namely, tinnitus, fullness in the head and ears and headache—were noted in minor degree and caused no interruption of therapy. One patient who gave a history of hypersensitivity to quinine was uneventfully treated with chloroquine.

### Discussion

Our experience indicates that chloroquine is easier to administer to the patient and does not have the yellow-dye discoloration effect of quinacrine. Clinically, it was no more effective in preventing relapses than quinacrine. The combined quinine and plasmochin regime has proved as effective in reducing the relapse rate over a prolonged follow-up period as Most et al.<sup>1</sup> found it to be. It is expensive and takes time, and yet is effective in returning the non-working patient to gainful employment. Under controlled observation no toxic manifestations of importance occurred. The abdominal cramps seemed to be relieved best by rest. Sedatives and antispasmodics were ineffective. We do not recommend the combination except under controlled observation and restricted activity.

It is interesting that all the patients with the proved cases of recurrent malaria admitted to the hospital, with 2 exceptions, came from the Pacific area—New Guinea and adjacent islands, the Solomons, Netherlands East Indies, Philippine Islands and Okinawa. The exceptions had been stationed in the China and India-Burma theaters. No patients from the Mediterranean or Caribbean theater were encountered. This is of diagnostic importance, since many patients from the latter theaters have been referred to the hospital with the erroneous diagnosis of malaria.

We continue to see patients who were last in a malarial zone a year and a half ago, entering with their primary delayed malarial attack. Many had lacked their usual sense of well-being since they returned from overseas and may have experienced slight attacks in the interim. Almost without exception these cases have not been recognized as malaria by physicians, and the patients were admitted to the hospital with diagnoses of fever of unknown origin or pneumonia. No cause for the lighting up of these dormant infections was elicited.

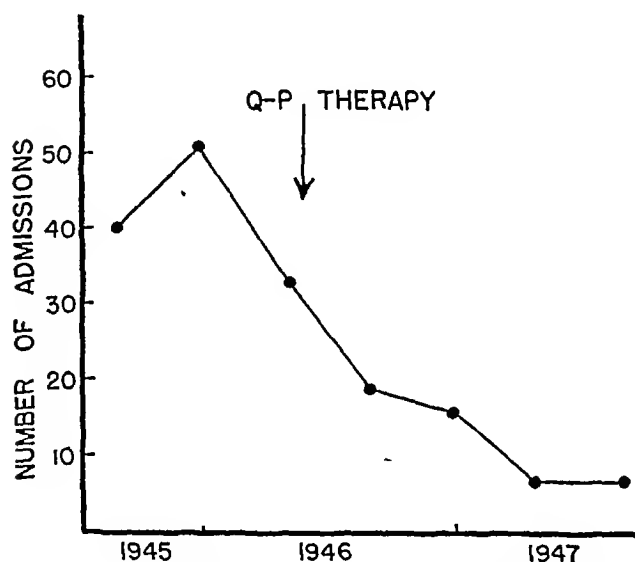


FIGURE 1 Monthly Admission Rate, Averaged Quarterly, of Patients with Proved Vivax Malaria (September, 1945, to July, 1947)

Conversely, the prophesied subsidence of the malarial attacks of Pacific origin after three or four years has been borne out by the admission rate. Figure 1 illustrates the monthly admission for proved malaria, averaged quarterly. The curve suggests a possible effect of the combined quinine and plasmoquin therapy on the recurrence rate, since prior to July 1, 1946, many patients had been hospitalized two or more times, the admission rate thus being elevated. In addition, the patients admitted during the past six months had acquired the infection in 1944 or later. Certainly the bulk of those who contracted the disease in 1942 or 1943 are no longer experiencing symptoms that can be proved to be due to malaria.

### SUMMARY

Chloroquine (SN 7618) was as effective and better tolerated than quinacrine (atabrine) in acute

malarial relapses or when used for suppressive therapy. It does not further reduce the relapse rate of malaria of Pacific origin.

The combined quinine and plasmoquin regime, under controlled observation and restricted activity, affords a safe and effective means of markedly reducing the relapse rate.

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## EXFOLIATIVE DERMATITIS DUE TO CODEINE\*

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CODEINE has been in use as a narcotic since 1832,<sup>1</sup> when it was first extracted from opium. Chemically, it is the methyl ester of morphine<sup>2</sup> containing a phenanthrene nucleus.<sup>3</sup> Today it is used in massive amounts, especially in sanatoriums, and yet drug eruptions due to sensitivity to this agent are extremely rare. Seidmann<sup>4</sup> stated that up to 1943 only 10 such cases had been reported in the literature. Since then at least 2 additional cases have been reported. The following case is presented because of the severity of both the skin and systemic manifestations.

### CASE REPORT

A 34-year-old man was admitted to the hospital with a diagnosis of scarlet fever. The past medical history revealed that the patient had had the usual childhood diseases a recurrent otitis media of a chronic nature and gonorrhea three times in the past 10 years. There was no allergic history. The family history was uncontributory. Six weeks before admission the patient had first developed a severe myositis of the shoulder, involving chiefly the trapezius muscle, for which he had received large daily doses of codeine, phenobarbital, salicylates and thiamine until the day of admission. About 7 days before entry he developed a mild generalized erythematous rash with a superimposed urticaria which caused a great deal of itching. This was unassociated with fever, sore throat or photophobia and subsided after 2 days. The erythema and urticaria recurred, however, 4 days later in a severer form and was associated with fever. The systemic review was essentially negative.

Physical examination revealed a well developed well nourished man. There was a generalized macular erythematous rash with numerous superimposed giant urticarial wheals from 2 to 8 cm. in diameter distributed over the entire body.

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Over the bridge of the nose and malar prominences there was a small punctate papulopustular rash which was apparently quite recent in origin. Examination of the ears revealed a perforated right drum. Otherwise the physical examination was negative.

The temperature was 104°F.

The patient was taken off all medication and treated symptomatically. He continued to run a septic type of fever for approximately 4 days, after which the temperature suddenly dropped to low grade levels. By the 2nd hospital day the punctate pustular rash previously noted over the nose and malar prominences had spread to involve the entire face and upper portion of the chest but advanced no farther. On the 3rd hospital day the urticaria subsided leaving large purpuric spots on the involved portions of the skin. Numerous small desquamating areas were also noted at that time on the lower arms and legs. Soon thereafter a generalized desquamation of flaky loose scales up to several centimeters in diameter developed. The patient also complained of marked diplopia and eyeball pain which however subsided after 3 days without residual symptoms and without recurrence. It was noted that the patient was extremely sensitive to temperature changes such as a very mild draft or change of bedclothes during which he developed a frank chill. There was a marked tremor of the extended hands as well as an intention tremor which also subsided as the patient improved. On the 8th hospital day the corium layer of the hands and soles of the feet was shed in glove-like fashion similar to that seen in scarlet fever. The desquamating areas began to weep considerable amounts of serous fluid. This was followed by crusting and continued desquamation. About the 12th hospital day a secondary skin infection involving the antecubital fossa and legs developed. This was followed by a marked rise in temperature up to 104°F., with leukocytosis and marked regional lymphadenitis. The patient was placed on penicillin therapy (40,000 units every 3 hours) intramuscularly and tyrothricin locally to involved areas after which the temperature dropped to normal limits within 5 days. Symptomatic therapy and penicillin prophylactically were continued. His condition gradually improved during the next month although a great deal of desquamation was noted.

After convalescence it was thought advisable to determine the origin of the dermatitis. Patch tests with codeine pheno-

barbital, thiamine and sodium salicylate, both solution (1:1,000) and the powdered form of the drug being used, were performed. There was no reaction to these tests. The patient was then given intradermal injections of 1:10,000 of the same preparations at 1-week intervals. There was no reaction to salicylates, phenobarbital or thiamine. However, 30 seconds after the injection of codeine a giant urticaria at the site of injection about the size of the palm of the hand, as well as a generalized urticaria, developed. This subsided after eight hours. However, by the next morning there was a marked purpuric spot in the area of the skin test, as well as a fine punctate pustular rash involving the face similar to that observed on admission. At that time considerable concern was caused by the fear that a recurrence of the dermatitis had been precipitated. However, the rash entirely subsided within 48 hours without further complications. The patient was discharged on the 70th hospital day.

Repeated urinalyses during hospitalization were negative, with specific gravities ranging up to 1.028. Because of the diplopia a spinal tap was done, which was also negative, as were repeated blood cultures. Agglutination studies for typhoid, salmonella and the brucella organisms were also negative. Routine blood studies revealed a red-cell count varying from 4,500,000 to 5,000,000 during hospitalization. The white-cell count on admission was 8200 with 3 per cent eosinophils, 11 per cent lymphocytes, 2 per cent monocytes and 84 per cent neutrophils. By the 14th hospital day, during the height of the secondary infection, the white-cell count rose to 19,000 with 11 per cent eosinophils, 15 per cent lymphocytes, 6 per cent monocytes and 68 per cent neutrophils. On the 30th hospital day the white-cell count returned to normal, showing only 1 per cent eosinophils. On the day of discharge the white-cell count and differential were normal. The serologic findings were negative. Throat cultures revealed *Staphylococcus albus*. Cultures of the secondarily infected areas were positive for hemolytic staphylococcus. Repeated x-ray films of the chest were normal.

### DISCUSSION

Pollak<sup>4</sup> first described a case of pinhead-sized papulopustular eruption due to codeine in a one-and-a-half-year-old child who had been receiving codeine for some time in a cough mixture. This was similar to the presenting facial rash in the case reported above, except that in the former case the rash was mild and quickly disappeared after withdrawal of the drug without further complications.

An itchy erythematous rash due to codeine that was similar to the urticarial erythematous rash on the trunk and limbs in this case and that later cleared after mild desquamation was described by Von Essen<sup>5</sup> in a thirty-one-year-old woman.

The most frequent finding in reported cases has been an erythematous scarlatiniform eruption, which the case reported above also exhibited.<sup>1-12</sup> This manifestation was very well described and discussed by Scheer and Keil,<sup>6</sup> who reported such a case. In their patient the patch test was positive to a solution of codeine but was negative when the powder was used. Palmer's<sup>3</sup> patient also had positive patch tests to 1:100 and 1:1000 solutions.

Although patch testing is rarely of value in dermatitis medicamentosa, it was thought justifiable to attempt to determine the etiology of this patient's dermatitis in view of successful reports.<sup>3, 6</sup> However, patch tests employing both the powdered drugs and the 1:1000 solutions were negative. Intradermal skin tests using 1:10,000 solutions were then employed. These were negative for thiamine, sodium

salicylate and phenobarbital, but there was a marked reaction to codeine. Scheer and Keil first noted that codeine injected intradermally gave a positive wheal in normal persons and that the intradermal test was valueless. We were not aware of this at the time we attempted to determine the etiology of this patient's difficulty. Although no deaths have been reported from codeine sensitivity, there seems little doubt that poor judgment was exercised in the use of intradermal skin tests in this case, since it is easy to imagine that a severe recurrence of the exfoliative dermatitis may have been precipitated by this procedure. However, the diagnosis seems well established in view of the recurrence, after the intradermal injection of codeine, of a generalized urticaria followed by a punctate papulopustular eruption of the face similar to the original eruption.

None of the previously reported cases have run such a toxic course, nor have the patients had so many and severe skin manifestations as this patient presented. These included pustular papules, erythema, urticaria, purpura and eventually generalized exfoliative dermatitis. The patient was desperately ill for approximately a month, and only by the use of antibiotics for the control of secondary infections and by considerable nursing care was he saved. The marked transient eosinophilia has been observed previously in this condition,<sup>1, 9</sup> but as noted above is not a common finding in drug eruptions.

### SUMMARY

A case of exfoliative dermatitis due to codeine is reported. The rash was manifested by a papulopustular eruption of the face and generalized macular erythematous rash with superimposed urticaria, which was followed by weeping in some areas and generalized desquamation. For forty days the patient ran a severe course complicated by secondary infection. After recovery a skin patch test was negative but the intradermal injection of a 1:10,000 solution of codeine caused a generalized urticaria and mild manifestations of the original picture. This was thought to be sufficient evidence to establish the etiology.

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## MEDICAL PROGRESS

## DIABETES (Concluded)

ELLIOTT P JOSLIN, M.D.\*

WITH THE CO-OPERATION OF LEO P KRALL, M.D.,† C C BAILEY, M.D.,‡ HOWARD F ROOT, M.D.,§  
PRISCILLA WHITE, M.D.,¶ AND ALEXANDER MARBLE, M.D. ||

## BOSTON

## PREGNANCY IN DIABETES

Pregnancy in diabetes continues to interest Dr Priscilla White,<sup>22</sup> and in an article presented before the Third Congress of Obstetrics and Gynecology, her conclusions were brought up to date

The typical course of a diabetic pregnancy as seen in diabetic clinics is the following one from conception to term the pregnancy has a 50 per cent chance for survival and terminating in a live birth. If pregnancies of diabetics are studied from viability on the chances for success increase to 65 rarely to 75 per cent. (The expected fetal survival at present is better than 90 per cent)

## The importance of vascular disease is stressed

Although fetal survival is possible with advanced arteriosclerosis, a review of our patients who had unexpected failures showed that when arteriosclerosis was so advanced that the arteries of the pelvis were calcified (30 cases), the chances for fetal survival were poor, 10 per cent. In 16 cases where every form of treatment we know was included, the survival rate to 19 per cent. Calcified pelvic vessels not revealed in the pre- or early pregnancy screening plates have been revealed in from 6 to 12 months after failures or stormy pregnancies. Intimal disease favoring occlusion — characteristic of diabetes — is inferred to be present before the calcium is deposited.

Seventy five per cent of our patients are delivered by Cesarean section, performed under spinal anaesthesia without preliminary sedation. Spontaneous normal deliveries are also conducted under spinal anaesthesia and with minimal sedation

For details of treatment of both mother and child, the original article must be consulted, but the following is a brief summary

The management of diabetes includes the prescription of diets high in carbohydrate 180 to 250 grams, high in protein 20 grams per kilogram of body weight, and fat to complete the caloric prescription of 30 calories per kilogram

Multiple doses of insulin protect the patient from the ketosis consequent to the low renal threshold for glucose and avoid hypoglycemia

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The treatment of the disturbed chemistry includes the use of ammonium chloride in doses of 4 to 8 grams daily acid ash, high protein diets. Sodium is restricted. The most important part of the treatment is the substitutional hormonal therapy.

Various routes of administration, types of therapy, durations of treatment have been employed but the best results in my experience have been with early and continuous stilboestrol and proluton intramuscularly. The present form of treatment is as follows:

Week of Pregnancy	Stilboestrol mg daily	Proluton mg daily
Up to 20th	5	5
20-24	10	10
24-28	15	15
28-32	25	25
32-38	50	50

Regulation of stilboestrol is controlled by serum levels of chorionic gonadotropin and proluton by urinary determinations of pregnandiol.

## METABOLISM OF CARBOHYDRATE AND FAT

An excellent summary of the work of the Coris and their associates at Washington University, St. Louis, was given by C F Cori<sup>23</sup> in his Harvey Lecture. It will be recalled that from these studies it became apparent that at least one site of action of insulin in the body is at the point at which glucose is admitted to the metabolic system by conversion to glucose-6-phosphate. This conversion of glucose takes place by reaction with adenosine triphosphate under the influence of a sulphhydryl enzyme, hexokinase. The Coris found that the hexokinase reaction was inhibited by anterior pituitary extract and that insulin opposed this inhibition. Insulin had no direct effect upon the reaction. Although not all the known facts can be fitted easily into the proposed scheme, a convincing demonstration of one site of action of insulin is now available. Stetten<sup>24</sup> regards Cori's work as of great significance and emphasizes the fact that once glucose has been phosphorylated, many pathways are open to it: it may be converted to glycogen or to fat, or it may be oxidized. Stetten and his co-workers<sup>25</sup> showed that in the well nourished rat, only about 3 per cent of the glucose ingested is converted to glycogen, whereas about 30 per cent (ten times as much) is consumed in the manufacture of fatty acids. More and more it is coming to be recognized that the metabolism of carbohydrate, protein and fat is not independent but that all three contribute to a common

metabolic pool to which active fragments are constantly being added and withdrawn. Investigation along this line is for the first time possible through the use of isotopes by means of which individual molecules can be labeled and traced through the body.

#### DIABETES SECTION OF THE UNITED STATES PUBLIC HEALTH SERVICE

The Diabetes Section of the United States Public Health Service was formed in recognition of the increasing public-health aspects of diabetes. There is a growing diabetic population, and indications are that only about half the patients have been found. To avoid complications of the disease, efforts must be made to find the others early and to start their education. The objectives of the Diabetes Section are to demonstrate the application of public-health measures in the early detection of the disease and to stimulate, encourage and support research in all aspects of diabetes, including the development of new laboratory methods and techniques.

Among the accomplishments of this section have been the Oxford Diabetes Survey cited above and two diabetes units. One is established in co-operation with the Florida State, Duval County and City of Jacksonville Health Departments. The second unit works in co-operation with the Commonwealth of Massachusetts and the Town of Brookline Health Departments. The project includes early detection of cases and dissemination of information about diabetes to the diabetic patient and to the public. Patients with newly discovered diabetes are referred to their family physicians for further study and treatment.

A new rapid screening test for blood sugar—described below—has been devised. Exhibits on diabetes have been presented at meetings of the American Public Health Association and sectional medical meetings and in co-operation with the American Diabetes Association at the annual meeting of the American Medical Association in 1947. Educational material is being prepared for general-population groups, health departments and the practicing physician in co-operation with the American Diabetes Association.

#### NEW RAPID BLOOD SUGAR TESTS

The Benedict test affords a simple and convenient method by which not only physicians but also diabetic patients may test the urine for sugar. Modifications such as the "Clinitest" and "Galatest" allow for even greater speed and convenience. It would be of tremendous advantage to all concerned if simple and quick methods were available also for the determination of the blood sugar. Some progress in this direction has recently been made. Hagedorn and his collaborators<sup>36</sup> have devised rapid modifications of their ferricyanide method, including a procedure in which most of the reagents are provided

in tablet form. A bedside method for the rapid determination of the approximate sugar content of the blood has been worked out by Leech and Woodford.<sup>37</sup> In this procedure, which requires a minimum of equipment and laboratory experience, blood proteins are precipitated by means of zinc hydroxide and the concentration of sugar in the filtrate determined by use of Sumner's dinitrosalicylate reagent. By either of these methods a blood sugar determination may be made within five minutes of the time of collection of the blood.

The third new method, developed by the Diabetes Office of the United States Public Health Service,<sup>38</sup> is particularly suited for rapid, large-scale screening tests in surveys and other studies of large population groups. The procedure is based on that of Hagedorn, but all reagents are in tablet form and the steps requiring experience in chemical techniques and all fluid reagents have been eliminated. Within five minutes a sample of blood (0.1 cc) can be classified as having above or below a certain glucose concentration.

With these new tests public-health departments have available means of early case finding, and the practicing physician can be materially aided in the better care of his diabetic patients.

#### ALLOXAN DIABETES

In previous years, attempts have been made to include in the progress reports<sup>39</sup> all references that have appeared on the subject of alloxan diabetes. The present article attempts to include all published reports on this subject since the previous summary in April, 1946. The subject has been extensively reviewed elsewhere.<sup>40-43</sup>

#### Chemistry

The chemistry of alloxan has been reviewed by Chen.<sup>44</sup> The diabetogenic action continues to be limited to alloxan and a few very closely related chemicals that may well change into alloxan once they are introduced into the body.

Brückmann and Wertheimer<sup>45</sup> report that *n*-methyl, ethyl and propyl alloxans, as well as alloxantin, dimethyl alloxantin, diethyl alloxan, dialuric acid and methyl dialuric acid, produce diabetes when injected into rabbits. Others<sup>46-48</sup> have shown that various ones of these compounds are diabetogenic, and Hidy<sup>46</sup> has stressed the fact that the intact pyrimidine ring is essential for the diabetogenic activity of any chemical compound such as alloxan.

Tipson and Ruben<sup>49</sup> claim that alloxan or its reduction product is present in the liver of normal animals and also describe their "purple" test for alloxan.<sup>50</sup> Karrer et al.<sup>51</sup> report a very sensitive test for the detection of alloxan and claim that this method will detect 0.5  $\gamma$  of alloxan per cubic centimeter of aqueous solution. Using this method, however, they were unable to detect any alloxan in the serum or urine of diabetic patients.

The experiments of Iyengar<sup>42</sup> suggest that alloxan experimentally acts as an activator for insulin

### Physiology

In addition to the rabbit, rat, dog, monkey, pigeon and turtle, diabetes has been produced with alloxan in sheep,<sup>43, 44</sup> hamsters<sup>45</sup> and cats.<sup>46</sup>

Shipley and Rannefeld<sup>47</sup> showed that the injection of small subdiabetogenic doses of alloxan could irreversibly alter the functional reserve of the islet-cell tissue, as demonstrated by the glucose-tolerance test. Animals so treated if then given anterior pituitary extract developed a markedly increased blood sugar.

With ordinary diabetogenic doses of alloxan there is complete functional recovery from initial kidney damage.<sup>48</sup> Duffy<sup>49</sup> found that the dose of 200 mg. of alloxan per kilogram of body weight intravenously in rabbits resulted in death in many of the animals. Some of those that survived, however, developed diabetic cataracts.

Lazarow and Palay<sup>40</sup> found the intravenous injection of 40 mg. of alloxan per kilogram of body weight in rats a satisfactory method of producing diabetes mellitus. The intraperitoneal route required larger doses.

The withdrawal of all foods from adult rats for a period of forty-eight to sixty hours before the injection of alloxan renders the animals more susceptible than the nonfasted animals to the diabetogenic action of alloxan.<sup>41</sup> According to Houssay and Martinez,<sup>50</sup> a low-protein or high-lard diet increases the rat's susceptibility to alloxan. The high-lard diet, however, loses its effects if methionine, thionin or coconut oil is added.

Levey and Suter<sup>51</sup> claim that the administration of ascorbic acid to rats increases the diabetogenic action of low doses of alloxan if the vitamin is given within one minute before the administration of alloxan. It has been stated that ketosis has been produced in alloxan-diabetic rats by means of a diet high in niacin.<sup>44</sup>

The initial hyperglycemia followed by temporary hypoglycemia that follows the injection of alloxan and precedes the onset of true diabetes has been discussed again.<sup>45</sup> Goldner and Gomori<sup>46</sup> present further evidence to support the hypothesis that the secondary hypoglycemia following the injection of alloxan is pancreatic in origin.

Canzanelli<sup>47</sup> found that, *in vitro*, alloxan has no direct effect upon liver glycogenolysis, and these findings therefore oppose the concept that the initial hypoglycemia of alloxan diabetes is a result of an effect of alloxan on the liver. It has been shown that alloxan inhibits muscle glycolysis and that this inhibition can be reversed by the addition of cysteine.<sup>48</sup>

The glycogen reserve of the muscles and of the liver in alloxan-diabetic rats has been approximately doubled by the administration of insulin.<sup>49</sup> Weber<sup>52</sup>

found that the glycogen content of the liver after twenty-four hours of fasting was higher in alloxan-diabetic rats than in normal rats, whereas the glycogen content of the muscles was lower.

Franks et al.<sup>71, 72</sup> believe that the rise in the plasma inorganic phosphates of alloxan-diabetic rats during diabetic coma is due to a breakdown of the liver organic phosphates associated with a deficiency of insulin. The acid and alkaline phosphatase activity is significantly increased after the development of alloxan diabetes in rats according to Drabkin and Marsb,<sup>73</sup> and the administration of insulin produces a decrease in the activity of both acid and alkaline enzymes.<sup>74</sup>

Dogs made diabetic with alloxan have a more severe diabetes and require much higher doses of insulin than dogs made diabetic by pancreatectomy, according to Thorogood and Zimmerman.<sup>75</sup> Although some believe that this results from decreased food absorption since the digestive enzymes are decreased in amounts, these workers postulate the possibility of a second hormone from the pancreas, the absence of which allows the diabetes to become more severe and predisposed to ketosis.

Foglia et al.<sup>76</sup> showed that depancreatized rats that later receive a diabetogenic dose of alloxan develop after the administration of glucose a hyperglycemia, which is more acute and of longer duration than when rats that have been depancreatized alone are given glucose.

The secondary transitory hyperglycemia that follows the injection of alloxan into dogs is markedly delayed in dogs in which a vagotomy-thoracotomy operation has been performed, according to Shipley and Beyer.<sup>77</sup>

Kendall and his associates<sup>78</sup> report a transitory period of hypercholesterolemia and hyperlipemia during the early stages of severe diabetes in rabbits injected with alloxan.

In 20 of 30 rabbits injected with alloxan by Herbut et al.<sup>79</sup> a very severe periportal necrosis of the liver occurred. The feeding of reduced iron to 2 diabetic and 2 controlled rabbits for two and a half weeks resulted in the deposition of iron in the liver and other organs. Attempts are being made to produce hemochromatosis by this method.

Rabbits made diabetic with alloxan that become pregnant have abortions, or premature delivery in half the experiments.<sup>80</sup> No evidence of an increased birth weight among the fetuses in diabetic rabbits was found, however. In rats made diabetic with alloxan, the pregnancies reach full term and result in the birth of healthy fetuses with normal birth weights. Injection of alloxan into pregnant animals appears to have no ill effect on the fetuses.

### Prevention

Soon after it was proved that alloxan could produce diabetes in animals attempts were made to find substances that would prevent its diabetogenic



action This was quite logical, for if alloxan had anything to do with the etiology of diabetes in human beings it would be quite important to find some substance that would prevent its action It has been known for a long time that alloxan has an especial affinity for the sulfhydryl group, and Lazarow<sup>81</sup> has shown that, if large doses of glutathione or cysteine are intravenously injected into rats immediately before the injection of a diabetogenic dose of alloxan, diabetes is prevented If, on the other hand, these substances are given one minute after the injection of alloxan only partial protection results If the injection is made three or four minutes after the injection of alloxan no protection is seen<sup>82</sup> Recently, it has been shown that BAL (British Anti-Lewisite) also prevents the diabetogenic action of alloxan in rats,<sup>83-85</sup> presumably because it too is a sulfhydryl compound

Banerjee<sup>86</sup> found that 100 mg of nicotinic acid per kilogram of body weight injected intravenously and followed by a like dose of alloxan protected 5 rabbits from diabetes When doses of 200 mg per kilogram were used, however, 2 of 3 rabbits developed diabetes

Clamping the kidney vessels in the dog before the injection of alloxan prevents the development of diabetes according to the report of Jimenez-Diaz et al<sup>87</sup> Other workers found that clamping the renal pedicle of rabbits or rats did not prevent the diabetogenic action of alloxan or the histologic changes in the islets of Langerhans<sup>88-90</sup>

Walpole and Innes<sup>91</sup> found that ligation of the main pancreatic duct in rabbits prevents the action of alloxan, but no other reports supporting or rebutting this finding have yet appeared

It has previously been reported that the injection of adrenalin intraperitoneally before the injection of alloxan prevented diabetes<sup>92</sup> LeCompte and Bailey<sup>89</sup> found that the injection of small quantities of epinephrine intraperitoneally into rats produced a marked constriction of the capillary and small blood vessels of the intact pancreas, which could be seen microscopically It is presumably the vasoconstriction that keeps the alloxan from reaching the islets of Langerhans and prevents the diabetes

It has been suggested that pentnucleotides act as an antagonist to alloxan in the rat<sup>93</sup>

### *Influence of Endocrine Glands*

Gaarenstroom et al<sup>94-96</sup> report that extirpation of the hypophysis in animals already made diabetic with alloxan leads to a marked decrease or even total disappearance of glycosuria and a fall in the blood sugar, in fasting animals After administration of sugar, the blood sugar rises again to high levels

Bailey and his co-workers<sup>97</sup> showed that if rats were hypophysectomized and then given alloxan, diabetes developed but was much milder than that in control animals given alloxan alone

Houssay and his associates<sup>98</sup> have studied the relation of the thyroid gland to alloxan diabetes quite extensively They report that thyroidectomized rats show a greater resistance to the diabetogenic and toxic action of alloxan than control animals and that thiouracil-treated rats show even greater resistance to alloxan

Experimental hyperthyroidism produced by the administration of thyroid extract increases and thyroidectomy decreases the sensitivity of rats to the action of alloxan<sup>99</sup> Dogs with transitory diabetes as a result of the injection of alloxan develop permanent diabetes when they are treated with thyroid extract,<sup>100</sup> but the administration of thyroid extract does not produce diabetes unless the islets of Langerhans have previously been injured A very unusual finding was that thyroid treatment of pancreatectomized rats in which diabetes had already become incipient caused its complete disappearance In spite of continued treatment, however, diabetes reappeared in a third of the animals The nontreated controls all eventually became diabetic<sup>101</sup>

Suarez Soto<sup>102</sup> also produced so-called "meta-thyroid diabetes" by administering thyroid extract to dogs whose pancreases had been handicapped by the administration of small doses of alloxan

No amelioration of alloxan diabetes was found when rats were treated with diethyl stilbestrol<sup>103</sup>

Janes and Friedgood<sup>104</sup> reported that when alloxan-diabetic rats were adrenalectomized a marked reduction or complete disappearance of diabetic symptoms resulted On further study of this problem, however, they found that the amelioration of the diabetes following an adrenalectomy was associated with a lowered food intake rather than the direct results of the adrenalectomy<sup>105</sup>

### *Pathology*

The pathology of alloxan diabetes has been described in a most complete article by Duff<sup>106</sup> Two new findings have been reported in the last year Duff et al<sup>107</sup> observed moderate to extreme hydropic degeneration of the pancreatic ductules and islets of rabbits made diabetic with alloxan after several months of diabetes Such changes were detected as early as forty-five days and were never absent after ninety days, provided the average fasting blood sugar level was 303 mg per 100 cc or higher These hydropic degenerative changes, both in the ductules and in the islets, are reversible if the diabetic state is treated with insulin

Proliferative changes have been described by Di Pietro<sup>108</sup> in the centroacinar cells of the pancreas and the intracanalicular ducts

Grossman and Ivy<sup>109</sup> believe that the vacuolization of the intralobular duct cells of the pancreas, along with their finding of decreased responsiveness to secretin, suggests that the small duct cells participate in the formation of pancreatic juice

### Clinical Considerations

The clinical implications of alloxan diabetes have been summarized by Bailey and LeCompte,<sup>110</sup> and the relation between experimental and human diabetes has been compared by Gale.<sup>111</sup> It has been pointed out that alloxan is a chemical with dangerous toxicity and its use in man at present is ill advised.

Since alloxan destroys the islets of Langerhans it was quite natural that it has been used in the treatment of hyperinsulinism. Talbot and Bailey<sup>112</sup> administered alloxan to an eight-month-old baby with the clinical and laboratory findings of hyperinsulinism, with somewhat encouraging results. This was done only after careful surgical exploration had failed to reveal any evidence of a pancreatic adenoma. The authors warn of the extreme dangers in the use of this drug.

The danger associated with the administration of alloxan in human beings has been well illustrated in a case of islet-cell carcinoma with extensive metastasis in which alloxan had been used as a last resort.<sup>113</sup> After three injections of alloxan the patient developed acute yellow atrophy and died with extensive liver necrosis.

Conn<sup>114</sup> reports that alloxan may destroy the normal islets of Langerhans in the pancreas. In the treatment of a case of hyperinsulinism with alloxan, no effects were noted on the pancreatic islet-cell adenomas, but the normal islet cells were damaged and the patient developed diabetes after the islet-cell carcinoma had been removed surgically. A biopsy of the pancreas in this case confirmed islet-cell damage.

Another case of islet-cell carcinoma of the pancreas with liver metastasis was treated with alloxan by Flinn et al.,<sup>115</sup> but no clinical effect from the alloxan was observed.

Uric acid diabetes is reported by Griffiths<sup>116</sup> of the Australian Institute of Anatomy, Canberra, Australia, as having been produced experimentally in rabbits. Recognizing that diabetogenic doses of alloxan, as well as minhydrin (though nondiabetogenic) lower blood reduced glutathione levels in rats appreciably, he administered uric acid parenterally with the thought that it might exert a diabetogenic action under such conditions. Intra-peritoneal injections of 1 gm of uric acid per kilogram of body weight into these deficient animals caused an initial hyperglycemia lasting about eight hours. Later, despite food, the animals remained hyperglycemic, and glycosuria persisted for the next four or five days. The blood sugar response resembled that which follows an injection of alloxan.

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The growth of interest in diabetes continues. Associations have been formed in the United States, England, France, Denmark, Belgium, Holland, New Zealand and Australia. In England and

France publications for the lay public are issued, appearing in three or four issues yearly. The American Diabetes Association inaugurated such a policy beginning with the issuance of the *ADA Forecast* in January, 1948. This blue-covered magazine has been designed with great care. It is especially to be commended because there are no advertisements. I am sorry not to feel at liberty to disclose the sponsors of the publications, who have had so much to do with making their timely appearance possible. *Diabetes Abstracts* and the *ADA Forecast* are certainly very forward steps in the dissemination of knowledge of diabetes for doctors, patients and the public and surely cannot but result in a notable advance in treatment.

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 3414

#### PRESENTATION OF CASE

A seventy-one-year-old man was admitted to the hospital because of orthopnea and ankle edema.

Ten years before entry he was treated in the Out Patient Department for late syphilis. Because of his age he was given bismuth only, and the blood Hinton test became negative. An x-ray film of the chest showed an enlarged heart and a tortuous aorta, with calcification of the aortic knob. Six years before entry he began to have dyspnea on exertion, and physical examination revealed an enlarged heart, with a regular rhythm, a soft apical systolic murmur (Grade II) and a soft aortic diastolic murmur (Grade I). He was digitalized and took digitalis irregularly ever since. The blood pressure was 140 to 150 systolic, 60 diastolic, the pulse 75-85, and the serologic tests for syphilis had been persistently negative. During the two weeks prior to admission he had severe dyspnea, with orthopnea and dependent edema.

Physical examination revealed a slightly cyanotic and icteric man. The neck veins were distended. There were fine, scattered rales in both lungs. The heart was enlarged, with the apex in the sixth space in the anterior axillary line. There were an aortic systolic (Grade II) and a diastolic (Grade I) murmur. The liver was enlarged and tender, and there was pitting edema of the lower legs.

The temperature was 100°F (rectal), the pulse 100 (irregular), and the respirations 24. The blood pressure was 145 systolic, 60 diastolic.

The white-cell count was 9300, with 70 per cent neutrophils. The hemoglobin was 13.5 gm. A van den Berg reaction was 0.9 mg per 100 cc direct, and 4.2 mg indirect (later 0.9 mg direct and 2.1 mg indirect). A cephalin-flocculation test was negative (later, +++ in forty-eight hours). The non-protein nitrogen, total protein and prothrombin time were within normal limits. Routine urine and stool examinations were negative.

An electrocardiogram showed auricular fibrillation and ventricular complexes arising from many different ectopic foci. A chest film demonstrated an

enlarged heart of aortic configuration, with calcification in the aortic arch, and congestive changes in both lungs.

The patient was treated with digitalis, ammonium chloride, mercurhydride and a low-sodium diet. Later, in view of the electrocardiographic findings, the digitalis was discontinued, and he was carried on 0.2 gm of quinidine daily. A good diuresis was obtained, and the pulse steadied to 70 to 80 per minute. However, he began to have anorexia, nausea and right-upper-quadrant tenderness attributed to distention of the liver capsule. One week after admission he suddenly developed pain in the right upper arm, which became cold, blue and pulseless. He was given spasmalgin and prepared for immediate embolectomy. However, in the interval the embolus passed farther down the arm, and operation was postponed. He was put on dicumarol and heparin, and the arm finally regained its normal circulation. The prothrombin time increased to 65 seconds (control 17 to 18 seconds), and the clotting time to 32 minutes. Two weeks after admission he developed repeated vomiting, which subsided the next day. He was given digifolin (1 cat-unit intramuscularly every other day) as well as the quinidine. He continued to have abdominal discomfort of varying severity without localization or tenderness and with negative x-ray studies. Four weeks after admission he suddenly had pain in the upper part of the abdomen and lower portion of the chest, restlessness, cold, clammy, dusky skin and a slow, irregular, weak pulse. The blood pressure was 80 systolic, 60 diastolic. There were a few rales in both lung bases, and the abdominal peristalsis was normal on auscultation. An electrocardiogram showed a rate of 65, a PR interval of 0.22 second, marked widening of the QRS complexes (0.29 second) and high T waves. The white-cell count was 19,200. Two hours later two examiners noted absent abdominal peristalsis. Both dicumarol and quinidine were discontinued. By noon the patient was much improved, ate well and had two stools. On the following day the white-cell count was 9800, the nonprotein nitrogen 67 mg per 100 cc, and the prothrombin time 36 seconds. The urine was normal, and the stools gave a ++ guaiac reaction. A few days later an electrocardiogram showed a more normal rhythm and rate, and a less prolonged QRS complex (0.16 second). A stool was negative for guaiac. The patient was again given dicumarol, and the epigastric distress returned, especially after the ingestion of food. He developed rapid fibrillation, with an apex rate of 120 per minute. He was given purodigin, and the pulse rate diminished to 84, and the pain subsided. He died a few hours later, one month after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: I always wonder how the experts grade murmurs, and, also, I always suspect that a soft murmur means a faint one, and a

harsh murmur, a loud one, but I am not sure of all this

I call attention to the fact that about three quarters of the bilirubin in this case was protein bound. I have called attention many times at these conferences to the fact that indirect bilirubin by the van den Bergh method means the total amount, including both that which requires the addition of alcohol and that which needs no addition of alcohol. Is that correct, Dr. Mallory?

DR. TRACY B. MALLORY: It must be.

DR. RICHARDSON: The direct test measures bilirubin that is not protein bound, and the indirect that which is due to protein-bound bilirubin. The finding in the case under discussion shows a slight increase of the blood bilirubin, most of which is due to protein-bound bilirubin. This is the significant point. One would expect to find some hemolytic process rather than an obstructive or intrahepatic process, although I do not think one can depend too much on this test.

The cephalin-flocculation test I am inclined to disregard, although probably I should not do so.

The nonprotein nitrogen at the time of entry was normal but later became elevated.

Digitalis was omitted — I suppose because of the ectopic beats and the suggestion of an irritable myocardium. Quinidine was given in small doses. It surprises me that, if the drug were used at all, more was not used. That amount may have been considered sufficient to prevent a sudden arrhythmia.

The clotting time may not be increased even though the prothrombin time is increased, but when the prothrombin time gets as high as that in the case under discussion, there is usually an increase in the clotting time too.

In the blood examination nothing is said about the distribution of the cells, and I have said much too much at these conferences about blood smears so that I will not say any more.

I think it is likely that the patient died of gastrointestinal hemorrhage. I want to say a few words about the use of anticoagulants. I am sure that I am a "stick-in-the-mud" regarding medicine and probably I am ultraconservative, but I should like to point out that when one uses anticoagulants and produces a prothrombin time of 65 and a clotting time of 32 minutes, one is adding a serious risk to the condition that the patient already has. I am not saying that anticoagulants should not be used when they are indicated. In some cases the calculated risk may be taken. But it seems to me that the pendulum has swung too far. I think it is fair to point out that a patient with a clotting time of 32 minutes is in constant danger of having a major vascular accident or major hemorrhage, as we know from our contact with hemophilic patients. There is a patient on the surgical wards now with a peculiar type of bleeding and a clotting time of 32 minutes,

and everyone is trying to bring that down. I do not want to go into the field of anticoagulants in phlebotrombosis, but I do think that we are going to find more and more cases in which increasing the prothrombin time has led to serious catastrophe or near catastrophe and in which the risk is not being clearly met. I am not doubting the integrity of those who use it and report on it, but it takes several years for the dangers to become apparent. Its use may have been justified in this case. This is the end of the sermon. I give it now, because I shall probably be wrong about this case and would not dare to talk about it afterwards.

What was this episode when the patient suddenly had upper abdominal pain? That is where the problem lies in this case. He became restless and had cold, clammy skin, a peculiar change in the electrocardiogram and an increased white-cell count. But in two hours he was very much better. What could have been the cause of this? My first and final thought was that he had a ruptured vessel, probably an artery. One might think of a pulmonary embolism. Why was it not a pulmonary embolism? It could have been, but it seemed to me to be rather a too rapid recovery. The white-cell count seemed to return to normal too rapidly. The same statement holds true for a ruptured viscus. If a viscus had ruptured into the abdominal cavity, I do not believe that the patient would have improved so much in two hours. The white-cell count of only 9800 may have represented a reaction to severe infection. I am unable to rule it out, but I doubt very much that it was infection. It may have been a hemorrhage into a closed cavity, such as rupture of an aneurysm, and that is a possibility that I cannot rule out. The thing that made me think of hemorrhage into the gastrointestinal tract was that he had had a great deal of abdominal pain, and something happened to intestinal peristalsis. I thought that loops of bowel might have been distended with blood. The nonprotein nitrogen rose to 67 mg per 100 cc, which did not seem explainable on the basis of shock because he did not appear to be in shock except for a very short period. One further explanation of the attack could be a coronary occlusion, with myocardial infarction. That is about all I can do except to say what the trouble was in the first place. He might have had a syphilitic aortitis. I think the evidence is against that because of the negative blood Hinton test. I assume that a Hinton test was done, although it is not mentioned that it was done in dilution and there may have been a so-called prezone phenomenon, if it were done in dilution, it would finally show up positive in the smaller dilutions.

DR. MALLORY: We know that the blood Hinton test was positive at one time and eventually became negative under treatment.

DR. RICHARDSON: I am taking the diagnosis of syphilis for granted. The problem is whether the

patient had syphilitic aortitis on admission, if so, the chances are that he would have shown a positive blood Hinton reaction. I do not believe that one can rule aortitis out, however.

He may have had subacute bacterial endocarditis. There seems to be little to suggest that disease other than the emboli. With this vascular setup he might, of course, have had periarthritis nodosa, which we frequently talk about at these conferences, I see nothing that points to it.

I have already mentioned the question of massive pulmonary embolism. He may have had that to start with, and the whole process may have been due to thrombosis of the pulmonary circuit. There does not seem to have been a cor pulmonale, the heart failure seems to have been more diffuse.

The sudden death, I suppose, may well have been a true cardiac death, and the whole thing cardiac from start to finish. I will postulate, however, that the underlying disease was arteriosclerotic—that the patient had a calcareous aortic valve, with coronary insufficiency, possibly associated with interference with the coronary intake at the coronary ostia, and that he had pulmonary infarction. I will explain the jaundice on the basis of the absorption of blood pigment from a fairly large infarction. I think he had, undoubtedly, auricular thrombi or, possibly, mural thrombi to account for the systemic circulatory embolism (unless one wants to believe that he had phlebothrombosis, with a very large, patent foramen ovale). Whether or not one has to consider intrinsic liver disease and whether one can explain the icterus on the basis of a congestive liver, I do not know, I suppose it is possible. At these conferences I am frequently given a case of liver disease to discuss, and this probably will turn out to be one. I am going to say, however, that this man had massive gastrointestinal hemorrhage, perhaps from an ulcer. He had calcareous aortic stenosis, coronary insufficiency, old pulmonary infarction, auricular thrombi and many other conditions.

A PHYSICIAN: Did the increase in clotting time occur after the administration of dicumarol or heparin?

DR RICHARDSON: I do not know. I assumed that the heparin was not continued. It was used for immediate effect until the dicumarol took hold. I assume that that could account for the increase in clotting time and not the heparin, but I do not surely know.

I forgot about the x-ray films. Perhaps we should see them now.

DR JAMES J. MCCORN: This is the chest film taken on admission. The left side of the heart is quite enlarged and probably represents an enlarged left ventricle. There is a plaque of sclerosis inside the aortic arch and a small amount of fluid in the costophrenic sinus. There is evidence of dilated vessels in the lung. This is the plain film of the abdomen, in which the liver does not appear to be

enlarged, there are no dilated loops of bowel. We have two films of the stomach, and they do not show evidence of ulcer.

DR RICHARDSON: I have no comment to make and no change in what I have said. I did not believe that there would be evidence of ulcer.

DR ALFRED KRAVES: Would Dr Richardson consider the possibility of coronary thrombosis superimposed on an old syphilitic aortitis to account for the embolism to one arm, in addition to the possibility of mesenteric embolism to account for the abdominal pain?

DR RICHARDSON: I agree. Very likely the emboli arose from a myocardial infarction. I thought of mesenteric arterial thrombosis, and I tried to say so but had too much language difficulty. However, I think that if the patient had had thrombosis of the mesenteric artery, he would not have been much better in two hours. On the contrary, he would have been much worse. Do you agree with that, Dr Cope?

DR OLIVER COPE: Yes, I think that is so.

DR RICHARDSON: Also, mesenteric thrombosis results in a very high white-cell count. I have seen it go up as high as 75,000 or 80,000.

#### CLINICAL DIAGNOSIS

Probable ventricular fibrillation

#### DR RICHARDSON'S DIAGNOSES

Calcareous aortic stenosis  
Coronary insufficiency  
Pulmonary infarction (old)  
Auricular thrombi  
Massive gastrointestinal hemorrhage (? ulcer)

#### ANATOMICAL DIAGNOSES

*Hypertrophy and dilatation of heart*  
Syphilitic heart disease, with aortic insufficiency, minimal  
Syphilitic aortitis, minimal, inactive  
Chronic passive congestion

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy did not explain all the findings. The primary underlying disease was in the heart, which was very much hypertrophied, weighing 720 gm., all the cavities and all four valve rings were uniformly dilated, and there was enough separation of the cusps of the aortic valve to make us believe that there had been syphilitic involvement. Seventy years is a very advanced age in which to see syphilitic involvement of the aortic valve. Patients with such a lesion ordinarily die at least a decade earlier than that.

Microscopical sections from the aorta showed some degree of vascularization of the media but almost no lymphocytic infiltration, which I think is consistent with a totally burned-out syphilis. There was no blood in the intestinal tract at the time of

autopsy, and nothing to explain the earlier episode of melena, which may have been due to dicumarol as Dr Richardson suggested. The liver showed a moderate but not severe grade of passive congestion. There were no pulmonary infarcts. The coronary arteries were patent. The lungs were acutely congested and edematous, as in cases of acute heart failure.

One other interesting finding that we see very rarely at autopsy was marked dilatation of all the lacteals in the duodenum and jejunum with fat-containing chyle. There was also a considerable amount of fat residue in the stomach. In medico-legal cases in which death is instantaneous, it is not rare to see lacteals containing chyle. We see it here not more than once in several hundred autopsies, presumably because the digestive processes slow down and stop many hours before the patient dies. That is a physiologic phenomenon, however, with no pathologic significance.

There was one peculiar finding, which I cannot explain—a few small foci of active hematopoiesis in the liver and a few more in the spleen. The bone marrow showed disproportionate activity of the red-cell series but a total cellularity that was rather below normal than above. This suggests that the patient had a moderate degree of blood dyscrasia, which I am unable to diagnose. The spleen weighed only 190 gm, which is well within normal limits, and it is unlikely that this was a hemolytic anemia.

DR KRANES: Then no source was found for the embolus in the arm?

DR MALLORY: No.

DR RICHARDSON: According to you, the patient is still alive.

DR MALLORY: He had a markedly hypertrophied and dilated heart.

DR RICHARDSON: He probably died of ventricular fibrillation or something of that sort. Perhaps the quinidine dosage should have been increased, but perhaps those treating the patient were afraid to do so because of the embolus.

DR MALLORY: The degree of aortic-valve involvement was minimal. I do not believe that one could blame the cardiac hypertrophy and failure on aortic insufficiency.

### CASE 34142

#### PRESENTATION OF CASE

A seventy-six-year-old widow entered the hospital because of inability to swallow.

The patient had been in excellent general health until about six months before admission, when she had an episode of abrupt syncope following a fall, with two similar episodes in the next few months, there were, however, no convulsions, and rapid recovery of consciousness followed each episode. One month before admission she noticed the abrupt onset of dysphagia followed by the inability to

swallow anything but liquids. She reported the presence of a crampy, substernal pressure sensation, which was relieved by regurgitation of undigested food. In the week before entry the patient noticed some bright-red blood streaking in the regurgitated material, but there had been no previous bleeding. There was no radiation of pain and no abdominal or systemic symptoms. She had lost a great deal of weight in the three weeks before admission but did not know the exact amount. She denied chest pain,



FIGURE 1

dyspnea, hemoptysis, ankle swelling, jaundice, melena or changed bowel habits.

Physical examination revealed a well developed, poorly nourished woman with a moderate memory defect who was coughing frequently but was in no obvious distress. Examination of the chest and abdomen was negative.

The temperature was 99.6°F, the pulse 100, and the respirations 26. The blood pressure was 130 systolic, 75 diastolic.

Urinalysis revealed a + test for albumin and rare red cells and 10 white cells per high-power field in the sediment. The hemoglobin was 12.4 gm, and the white-cell count was 9000, with 86 per cent neutrophils. The serum protein was 5.7 gm per 100 cc, the chloride 104 mEq per liter, and the nonprotein nitrogen 22 mg per 100 cc. The sedimentation rate was 23 mm in one hour.

X-ray films of the chest revealed elevation of the right side of the diaphragm, with partial fixation and fluid in the right costophrenic angle. There were areas of haziness and mottled density throughout the entire right lung field, with an area suggesting infiltration in the first and second interspaces, the left lung field showed mottled areas of density. The left main bronchus was well seen, but the right was not visualized. A barium swallow demonstrated a smooth, fusiform narrowing in the esophagus for a distance of 5 cm just below the carina (Fig 1), but there was no evidence of shelf formation, destruction of the mucosa or ulceration. Passage of barium was delayed, but there was no true obstruction.

Bronchoscopy demonstrated a concentric constriction below the right middle-lobe orifice, but no biopsy was obtained. Esophagoscopy demonstrated an obstruction 19 cm from the upper gum, which appeared diffuse and granular. The biopsy was reported as showing chronic inflammation. Cytologic examination of the sputum was reported as doubtful.

During the period of study the patient deteriorated rapidly. She developed anxious, gasping respirations and duskeness of the nail beds, ears and nose. Laminograms of the right lower-lobe bronchus showed an apparent area of narrowing about 1 cm below the upper-lobe orifice. Later chest examination demonstrated dullness over the entire right side, with absent breath sounds over the upper third. Another examination of the sputum on the fourteenth day was negative for tubercle bacilli but positive for tumor cells. The patient went downhill progressively and died on the eighteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

Dr EDWARD D. CHURCHILL: Inasmuch as no statement is made to the contrary, I assume that there were no neurologic residua to the episodes of syncope. They sound like manifestations of cerebral arteriosclerosis or vascular insufficiency. We might inquire about the radiation of pain in the chest. Radiation to the back comes from certain mediastinal lesions.

Loss of weight, presumably, is determined by reduced dietary intake. Of course, a patient who cannot swallow anything is going to lose weight.

The sedimentation rate was 23 mm in one hour. Is that a normal rate?

Dr MARIAN W. ROPES: That is a definite increase in sedimentation rate.

Dr CHURCHILL: What I should like to know is whether that rate was normal for a woman seventy-six years of age who was losing a good deal of weight.

Dr ROPES: The sedimentation rate should not be elevated because of weight loss.

Dr CHURCHILL: But you are not sure?

Dr ROPES: No.

Dr CHURCHILL: I do not like the word "partial" fixation of the diaphragm. I consider fixation an absolute term. The diaphragm either was fixed or it was not fixed. Is there any further statement about that in the record?

Dr STANLEY M. WYMAN: The diaphragm was fixed peripherally but moved centrally.

Dr CHURCHILL: Then part of the diaphragm was fixed. The qualifying adjective "partial" refers to diaphragm, not to fixation. Would you mind showing us the films now?

Dr WYMAN: The single film of the chest available shows the right leaf of the diaphragm to be elevated. It was fixed laterally and moved much less freely centrally than the left leaf did. The area of density described is best seen in the right lower-lung field, it also shows in the right upper-lung field, where there seems to be localized consolidation or density in the region behind the second rib. The areas of fine linear density in the left lung field one might expect in a seventy-six-year-old woman. The heart is a little larger than normal, without characteristic configuration.

Dr CHURCHILL: Is there fluid in the right costophrenic angle?

Dr WYMAN: Yes, and possibly a small amount in the left.

Dr CHURCHILL: The left main bronchus was well seen, but the right was not visualized. Barium demonstrated narrowing in the esophagus.

Dr WYMAN: These spot films best demonstrate the area of narrowing of the esophagus, just below the carina. The narrowing appears to be distensible and to change in contour, suggesting that it is flexible. The left main bronchus is well seen on the spot films, but the right is not visualized beyond the bifurcation of the trachea. In this view a short segment of the right main bronchus is seen that seems to taper. I can see no evidence of ulceration of the esophageal mucosa and no shelf formation.

Dr CHURCHILL: What is shelf formation?

Dr WYMAN: It is the term used to describe, somewhat inaccurately, the margin of a tumor mass, which may represent intrinsic or extrinsic tumor pressing on the esophagus or growing in the wall. It is seen, unfortunately, in inflammatory conditions also and is not, per se, a sign of tumor.

Dr CHURCHILL: The passage of barium was delayed, but there was no true obstruction?

Dr WYMAN: That is correct.

Dr CHURCHILL: The films of the stomach show how easily barium filled the stomach.

Dr WYMAN: We have a satisfactory examination of the stomach and duodenum. The esophageal delay is apparent in the spot film taken in the upright position. The esophagus can be seen proximal to the narrowing. It is not dilated as in a true obstruction. The stomach itself shows no disease. The duodenal cap and proximal duodenal loop are normal except for a diverticulum. There



are a few areas of calcification in the region of the right kidney, which are probably renal calculi

DR CHURCHILL Laminograms of the right lower-lobe bronchus were done. May we see them?

DR WYMAN This is the film that shows the lesion best, although it is not ideal. One can trace the left main bronchus quite readily and the right main bronchus for a short distance from the bifurcation. The upper-lobe bronchus is seen coming off and it appears of good contour. The lower-lobe bronchus is poorly visualized and is definitely narrowed in a fusiform manner. I cannot make out a mass in this region. The pleural fluid has increased considerably since the first observation.

DR CHURCHILL Later on, dullness is described over the entire right side of the chest, with absent breath sounds in the upper third. The physical findings were therefore changing, and there was increased fluid in the chest.

DR WYMAN Yes.

DR CHURCHILL This woman was bronchoscoped, and it was observed that she had a concentric constriction of the right middle-lobe orifice. No biopsy was obtained at that time. Later, an esophagoscope was passed, and a biopsy obtained. The report of "doubtful" is of no help.

This history is obviously a trap. There are just enough findings in it that are atypical for carcinoma to make one reluctant to swing with the laboratory to a positive diagnosis of cancer. First of all, the x-ray peculiarities have been pointed out and, also, the negative findings on both bronchoscopy and esophagoscopy. If we are to resolve the problem by a diagnosis of tumor on the basis of the identification of tumor cells in the sputum, we must postulate a primary tumor in the bronchus, with secondary mediastinal involvement by metastatic disease. Cancer, primary in the esophagus, may involve the left primary bronchus. It does not involve the right primary bronchus below the level of the middle-lobe bronchus unless extraordinarily far advanced. The diagnosis of cancer of the esophagus has been made by bronchoscopy when the tumor was penetrating the left primary bronchus. But I doubt on anatomic grounds that the primary growth by direct invasion would pick off these two areas. One possibility, then, is primary bronchiogenic carcinoma in the right lung, with mediastinal extension or metastases producing secondary obstruction to the esophagus. Another is that this whole picture was caused by metastases from a primary focus elsewhere in the body. We have seen cancer of the cervix — a very small early carcinoma of the cervix — manifest itself by obstruction to the esophagus in just this area by spreading up through the retroperitoneal lymph nodes to the mediastinal lymph nodes. No mention is made of an extra-thoracic focus of neoplasm in the case under discussion. I do not know whether or not complete physical examination included visualization of the

cervix and precise examination of other likely areas of primary neoplasm in a woman of this age. We would like to see a statement that the breasts, for example, were not involved. We have to assume that the physical examination was complete and negative.

So far as differential diagnosis between neoplasm and inflammation is concerned, there is a great deal in favor of inflammation, particularly the nature of the lesion of the esophagus. It is described as a long, attenuated lesion, without obstruction. It is as though the esophagus were being gripped in a chronic, sclerosing, inflammatory lesion. What that could be is hard to say. We do know that tuberculosis produces such a lesion. We have had cases at these conferences in which tuberculosis of the mediastinum caused a similar picture. It is likely to occur in elderly persons. In favor of tuberculosis is the apical lesion pointed out by x-ray examination. The other lesions in the lung parenchyma could have been caused by esophageal regurgitation with food and mucus running down the windpipe and producing pneumonitis in this area of the lung. It would not account for the fluid in the pleural space unless there was an active pneumonia. There should also have been some signs of invasive infection from pneumonia.

Sputum examination was negative for tubercle bacilli but positive for tumor cells. On that evidence we must take the position that this lesion was not inflammatory but neoplastic. The statement that tumor cells have been demonstrated in the sputum is a definite one. There are cases in which the cytologic evidence can be taken as positive evidence. There are others in which we may have to put cytologic findings on a par with other clinical findings. Malignant cells were demonstrated in the sputum, so that the diagnosis must conform to that evidence and we must take the position that this woman had a cancer. All we can do is point out that there are many aspects of this case in which, in the absence of that finding, we would incline toward an inflammatory lesion — tuberculosis. Except for tuberculosis it is very difficult to picture an inflammatory lesion with a normal white-cell count and a normal temperature producing this type of process. The accumulation of fluid worries me a little, whatever diagnosis we accept. I wish we knew what it was — whether it had been aspirated, which would be another chance to demonstrate tumor cells, if it was a carcinoma.

With the evidence as presented, we can do no more than say that positive evidence of malignant cells, with the story and x-ray findings, allows no other tenable diagnosis than cancer. I expect it to be primary in the right bronchial tree, involving the esophagus by direct invasion and metastatic spread. In the absence of the positive findings of a malignant lesion, I would have leaned toward an inflammatory lesion, most likely tuberculosis.

A PHYSICIAN How about the syncope?

DR CHURCHILL It is described as syncope following a fall. I suspect that the fall was caused by the syncope. A cerebral arteriosclerosis was manifested in the hospital by memory defect.

A PHYSICIAN Could it have been tumor of the brain?

DR CHURCHILL Without localizing signs, I would not make a diagnosis of such a tumor.

DR KING These reports on tumor cells are checked by the head of the Vincent Laboratory, who has had much experience with this procedure, and when the report comes back positive I hate to throw it out. I think in this case the report came through very late in the course of study, but it did corroborate our opinion that the disease was neoplastic and not inflammatory. Where it had originated, we could not tell. The patient was too sick to go through many examinations to determine the source. She developed fluid quite rapidly just before death.

#### CLINICAL DIAGNOSIS

Carcinoma of esophagus

#### DR CHURCHILL'S DIAGNOSIS

Bronchiogenic carcinoma, primary in right lower lobe, with secondary involvement of esophagus  
Cerebral arteriosclerosis?

#### ANATOMICAL DIAGNOSES

*Bronchiogenic carcinoma, right lower-lobe bronchus, with extension to esophagus and metastases to mediastinal lymph nodes, liver and omentum*  
Thrombosis of pulmonary artery, right lower lobe  
Arteriosclerosis, generalized, severe  
Hydrothorax, bilateral  
Duodenal diverticulum

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Autopsy showed extensive carcinoma, and the problem to be settled is where it was primary. The two largest masses of tumor were found in the right lower lobe and an annular mass that encircled the esophagus. There was a secondary, entirely separate lesion of the esophagus as well. The tumor in the esophagus had invaded and involved the scrota and muscularis but at no point the mucosa, and there was no point of ulceration, which would be extremely unusual in a primary cancer of that area. The right lower-lobe bronchus was completely surrounded by tumor, and there was widespread extension of the tumor through the lung via the lymphatic channels. The findings there were consistent with primary bronchiogenic carcinoma of the right lower-lobe bronchus. Although no point of ulceration in the bronchial mucosa could be demonstrated, the bronchus became rapidly and completely stenosed.

Histologic examination, which does not help us any further, disclosed a wildly undifferentiated tumor, and it is quite impossible to say whether it arose from squamous or glandular cells. A few of the cells were vacuolated and might suggest mucin production, but we were unable to prove that to our satisfaction. There were metastases in the mediastinal lymph nodes, in the mesentery and in the liver. We were not able to examine the brain, so that we cannot say whether it contained metastases. Our final diagnosis was bronchiogenic carcinoma, right lower-lobe bronchus, with secondary involvement of the esophagus.

DR CARROLL C MILLER Did the X-ray Department believe that the haziness and the irregular areas represented lymphatic spread?

DR WYMAN The original interpretation was that the haziness in the right lung was suggestive of lymphatic metastases.

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## SAVING THE NEWBORN INFANT

A COMMUNICATION published elsewhere in this issue of the *Journal* calls attention to a most progressive step that has been taken in behalf of the newborn infant. This step, another important undertaking of the American Academy of Pediatrics, is the establishment in every state of the union of committees to develop and improve facilities for the hospital care of newborn infants.

The need for this action was indicated by Dr. Stewart H. Clifford\* in a paper read before the Massachusetts Medical Society in May, 1947, calling attention to the greatly increased demand for hospitalization of obstetric patients and the alarming increase in communicable diseases of the newborn.

\*Clifford, S. H. Diarrhea of newborn. *New Eng J Med.* 237: 969-976, 1947.

Dr. Clifford is chairman of the central committee on the fetus and newborn of the American Academy of Pediatrics.

These new committees wield no rubber stamps. They are out to produce results, both on their own initiative and in holding up the hands of public-health authorities. In Massachusetts the Department of Public Health has been preparing a new set of regulations for nursery construction and operation. The state committee will participate in such planning, and will co-operate in every other way with the Department.

As a useful guide to be followed voluntarily by hospitals until such time as these regulations may be put in force, Regulation 35 of Chapter II of the New York State Sanitary Code, enacted in January, 1948, is recommended for use, and is printed in the communication to which reference has been made. This regulation embodies the best known precautions that may be used for the control of diarrhea of the newborn infant.

## CANCER-DETECTION CLINICS

IN THE desire to do all possible in controlling cancer there have been evolved several types of cancer-detection clinics, and a great popular interest has been engendered in them. In fact any state that does not contain one or more of these clinics tends to be looked upon as decidedly backward in its cancer program. Forty of the states now have clinics of this type, and some four hundred of them exist altogether.

Both the American Medical Association and the American College of Surgeons have recognized the desirability of these clinics and have laid down certain principles for their establishment and operation.

The purpose of the clinics is essentially to examine healthy persons to determine whether or not they are harboring precancerous conditions, early cancer or other incipient pathologic processes. An analysis of the clinics was presented at the annual meeting of the New England Surgical Society on October 4, 1947, by Dr. Charles L. Larkin, of Waterbury, Connecticut, who pointed out a number of fallacies in the fundamental thesis of their operation.

To carry out annual examinations of the type proposed by some enthusiasts would require the entire time of every doctor in the United States, according to Dr Larkin. The cost would be at least one and a quarter billion dollars a year. The clinics as operating at the present time defeat their very purpose in that prospective examinees are booked for months ahead, and hence delay is encouraged should any symptoms appear in the interim.

The popularity of these clinics however, is so great that in all probability, since Massachusetts is one of the few states that does not have one, one or more will be organized by lay groups if the medical profession does not act.

There is no question that the most effective place for a cancer-detection examination is the office of the private physician. However, it is far from certain what types of diagnostic procedures are best suited to detect early cancer and what costly accessory services, such as x-ray and laboratory procedures, are warranted.

There has been proposed by the staff of the Palmer Memorial Hospital and recommended by the Committee on Cancer of the Massachusetts Medical Society and approved by the Council of the Society the establishment of a new type of cancer-detection clinic at the Palmer Memorial Hospital. This clinic would have as its primary purpose not the examination of a few hundred persons a year to determine whether or not they had cancer, which would be of little significance in the over-all problem, but rather would attempt to determine procedures in cancer diagnosis that would be of value to the practitioner and would so evaluate the laboratory and x-ray services as to enable those most useful to be selected and to avoid the expense of a wide range of laboratory and radiologic procedures.

It is important to keep in mind that all a cancer-detection clinic provides is an opportunity for a thorough physical examination with ancillary services. Properly organized, these clinics do not conflict with already existing tumor clinics or cancer clinics because the detection clinics are concerned primarily with healthy persons whereas the patients referred to the cancer clinic or tumor clinic already have developed a lesion.

A cancer-detection clinic of the type suggested for the Palmer Memorial Hospital might well not only be a very real asset to the practicing physician but also set a more realistic and practical pattern for such clinics throughout the country.

## A STEP FORWARD

A MEDICAL rehabilitation clinic in Boston has been planned, and a petition requesting incorporation has been filed. The purposes of the proposed clinic are as follows:

To maintain a charitable medical rehabilitation clinic or clinics for the benefit and treatment of convalescent patients to assist in the restoration of such patients to gainful economic independence to maintain facilities for the evaluation restoration and improvement of the remaining physical abilities of persons crippled or handicapped as a result of war, disease, accident or other causes referred to it by government and civilian hospitals, industrial and other clinics and by members of the medical profession.

This new type of medical clinic was originally conceived by one of our ablest and most respected statesmen, Mr. Bernard M. Baruch. He recognized the gap that existed in medical care between the time the patient left the hospital and the time he resumed normal routine productive activity. In 1944 he established The Baruch Committee on Physical Medicine,<sup>2</sup> which, working with a civilian scientific advisory committee and with representatives of the surgeons general of the armed forces, developed a plan based on the program of convalescent training and reconditioning treatment in military and naval hospitals, but also applicable to civilian communities. In 1946 the report on A Community Rehabilitation Service and Center<sup>3</sup> was published by the Baruch Committee on Physical Medicine. This stimulated in communities great interest toward the establishment of medical facilities or clinics that might specialize in the treatment of the seriously disabled convalescent patient.

New York University College of Medicine has already established a Department of Rehabilitation with Professor Howard A. Rusk as chairman. He will direct the project planned as part of the New York University-Bellevue Hospital Medical Center. The College of Physicians and Surgeons of Columbia University has placed Dr. Frank E. Sunchfield in charge of its recently affiliated Institute for Crippled

and Disabled Toronto, Canada, has a state-operated rehabilitation center that appears to be functioning not only for medical treatment of convalescence but also for active vocational guidance and training. Cleveland and Milwaukee have had rehabilitation workshops operating successfully for a number of years. Bridgeport, San Francisco and Kansas City have, or are now establishing, rehabilitation centers. Although Boston has one medically supervised rehabilitation center operated for the benefit of the clients of one insurance company only,<sup>4</sup> it needs one open to the public.

The Council of the Massachusetts Medical Society passed a resolution on May 24, 1947, recognizing the need for a rehabilitation center in Boston. Pursuant to this resolution, on February 26, 1948, a petition requesting the incorporation of The Bay State Medical Rehabilitation Clinic was filed with the Department of Public Welfare. The authorities are urged to grant this petition, so that the Commonwealth may have an opportunity to provide for its physically handicapped citizens some of the newer concepts of medical rehabilitation. The Division of Vocational Rehabilitation of the Department of Education could utilize the services of this new nonprofit private charity. The charter provides for the training of personnel, many of whom will be qualified to staff similar centers in other communities. The disabled citizens of Massachusetts should have medically supervised rehabilitation services as good as or better than those of other states. There is no reason why this new type of medical charity should not be granted incorporation promptly.

Many permanently disabled citizens can be rehabilitated to gainful economic self-sufficiency. It takes courage to start a new charity at the present time. The Commonwealth will benefit by the establishment of such a clinic. The people of Boston need this medical service.

#### REFERENCES

1. Agreement of Association of The Bay State Medical Rehabilitation Clinic on file with the Department of Public Welfare, Commonwealth of Massachusetts.
2. Report on "A Community Rehabilitation Service and Center" 24 pp. New York: The Baruch Committee on Physical Medicine, 1945. P. 5.
3. Report on "A Community Rehabilitation Service and Center" 24 pp. New York: The Baruch Committee on Physical Medicine, 1946.
4. Aitken, A. P. Rehabilitation of employee injured in industry. *New Eng J Med* 237:903-905, 1947.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

McOWEN — William H. McOwen, M.D., of Newton Upper Falls, died on March 9. He was in his eighty-seventh year. Dr. McOwen received his degree from Harvard Medical School in 1883. For sixty years he was a member of the staff of Newton Hospital.

Four daughters, two sons, seventeen grandchildren and two great-grandchildren survive.

ROBINSON — Leon J. Robinson, M.D., of Palmer, died on February 1. He was in his forty-second year.

Dr. Robinson received his degree from Boston University School of Medicine in 1934. He was a member of the staff of Monson State Hospital and was a fellow of the American Medical Association.

Two sisters survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### PROPER USE OF GAMMA GLOBULIN

The decision of the physician to use gamma globulin to prevent measles calls for the critical consideration of many factors. The indiscriminate use of the material on all children who have been exposed to measles is entirely unwarranted. Indications for various age groups may be summarized as follows: under six months prevention is unnecessary if the mother has had measles but is indicated if there is no history of measles in the mother, six months to three years (measles is most dangerous in this period) prevention is recommended, and over three years (measles is relatively mild with present available therapy) prevention is never justified, except in special circumstances such as sick or debilitated persons of any age or in children's institutions or hospital wards where it causes many cross infections. The use of gamma globulin for modification of measles in this or older age groups is justified.

Measles in a healthy child almost always confers lifelong immunity and causes at the most a loss of two weeks' play or school in the lower grades. Passive prevention at this age may mean that the person will later have measles — perhaps more severely as an adult — at a time when it can mean the loss of a semester's work in high school or college, or serious loss of employment.

The use of gamma globulin in other diseases, for which no evidence of efficacy has accumulated, is considered a waste of a very expensive product. Present stocks are derived almost entirely from fractionation of the large amounts of surplus plasma left over from the wartime Red Cross plasma program. This globulin should be conserved, since there is as yet no source of whole blood in view sufficiently large to supply future needs. If present supplies are exhausted, physicians will be obliged

to purchase the globulin, since the Department of Public Health has no funds for this purpose.

A circular giving more detailed information regarding the use of gamma globulin will be furnished on request to the Division of Biologic Laboratories, 375 South Street, Jamaica Plain 30, Massachusetts.

## MISCELLANY

### FEDERAL SECURITY AGENCY CHILDREN'S BUREAU

Dr. Samuel M. Wishik, formerly of the New York City Health Department, has been appointed to the Children's Bureau of the United States Federal Security Agency to direct the planning work connected with the Bureau's program of grants-in-aid to the States for maternal and child health and for crippled-children's services.

In announcing the appointment Dr. Martha M. Eliot, associate chief of the Children's Bureau, said that more effective health services are needed for the thousands of babies born prematurely and the children suffering with cerebral palsy, rheumatic fever, hearing defects, cleft palate and many other handicaps.

### ATOMIC ENERGY COMMISSION CANCER RESEARCH

The Atomic Energy Commission, according to a Washington Report on the Medical Sciences, has released its plans for the expenditure of \$5,000,000 that it received from Congress last fall for cancer research. Most important of its activities will be provision of free radioisotopes to qualified handlers in approved institutions, financial support of research projects in hospitals, clinics and universities, establishment of cancer investigation facilities at four Commission-operated laboratories and continued aid to the Committee on Atomic Casualties of the National Research Council. This committee is investigating long-term effects on survivors of the Nagasaki and Hiroshima bomb explosion.

### AMERICAN PSYCHIATRIC ASSOCIATION

Dr. Daniel Blain, formerly chief of neuropsychiatric services for the Veterans Administration, has accepted the newly established position of medical director of the American Psychiatric Association. The position has been created to provide the full-time services of a physician who will act for the Association as an authorized source of information and advice.

As medical director, Dr. Blain will make his services available to the members, to affiliate societies and to public and private organizations interested in the field of psychiatry. He will serve also to effect liaison with the public on subjects related to the work of the Association and to the general interests of society.

For the present, Dr. Blain may be addressed at Georgetown University Hospital, Washington, D. C. or at the executive office of the American Psychiatric Association, Room 924, 9 Rockefeller Plaza, New York City 20.

### APPOINTMENT OF SOCIAL-SERVICE WORKER AT HARVARD SCHOOL OF PUBLIC HEALTH

As part of a new program to study the role of family life in the health of children, the Harvard School of Public Health recently announced the appointment of Miss Eliza Beth P. Rice, at present clinical professor of the social aspects of medicine at Yale University School of Medicine and assistant professor of the social aspects of nursing at the Yale School of Nursing as the first social-service worker to the faculty.

As assistant professor of medical social work in the Department of Maternal and Child Health, Miss Rice will begin a study of the preventive aspects of social work. Particular

emphasis in the new program will be placed on the role of the family in preventing the development of undesirable social habits in children. Also, attention will be directed to discovering unfavorable social factors as they relate to the health of the family.

Miss Rice, a native of Boston, received the A.B. degree from Wellesley College and the A.M. from Simmons College. Among the positions that she has held in the field of medical social work are assistant director of the Social Service Department, Boston City Hospital and director of social service, Boston Dispensary, the New Haven Hospital and the Grace-New Haven Community Hospital. She is the author of several publications on the part that medical social work plays in medicine and nursing.

## PROGRESS IN DENTAL MEDICINE

The Division of Dental Health of the Massachusetts Department of Public Health has completed the first year of its existence. During this period six studies concerned with the prevention of dental caries were in operation and water-fluorination programs were established in the Belchertown and Wrentham State schools with the Fernald State School as a control.

At the Daniel Butler School in Belmont a project has been started with the use of indium nitrate as a substitute for the fluorine salts in topical applications. In Brockton a study was set up on the effect of fluorine incorporated in dentifrices, in Medford one on the use of fluorine in mouth washes and in Quincy one on the incorporation of fluorine in prophylaxis pastes to be used twice yearly on a group of children.

At the Harvard School of Dental Medicine the announcement has been made of the promotion of Dr. Reidar F. Sognnaes, an authority on dental decay, to an associate professorship of dental medicine.

## CORRESPONDENCE

### COMMITTEE ON FETUS AND NEWBORN INFANT

To the Editor: The following physicians have been appointed by Dr. James M. Baty, state chairman of the American Academy of Pediatrics, to serve as a Massachusetts Committee on the Fetus and Newborn Infant: W. Bradford Adams, Springfield; Fred H. Allen, Holyoke; Joseph Garland, Boston; Paul J. Jakma, South Boston; Robert T. Moulton, Salem; Alfred S. O'Connor, Worcester; Herman Petterson, Boston; Clement A. Smith, Boston; Stuart F. Stevenson, Boston; and Alfred Weller, Arlington Heights. It is felt that readers of the *Journal* should be informed about the existence and function of this committee.

The American Academy of Pediatrics is setting up in all the states committees similar to this one with the purpose of developing and improving facilities for the hospital care of newborn infants—full term and premature. These committees will act in co-operation with the state and local public health authorities as representatives of the practice of pediatrics as it touches related interests in this field. Although many of the problems to be attacked will not be those of infectious diseases in the newborn period, the prevalence of sporadic epidemics of diarrheal disease in newborn nurseries will obviously turn a considerable part of the committee's attention to that special subject.

Dr. Stewart H. Clifford, chairman of the Academy's national committee in this field, has called attention to the recently approved New York State Sanitary Code bearing upon diarrhea of the newborn. Dr. Clifford and members of the committee believe that the New York statement is so admirably succinct and complete that it is transmitted as deserving publication. It has obviously no legal status in Massachusetts but covers the problem so well that it might be highly useful to any hospital or physician faced with the prevention or management of an epidemic and is offered only with this purpose. The code is as follows:

#### CHAPTER II

Regulation 35. Precautions to be observed for the control of diarrhea of the newborn. It shall be the duty of administrators of general hospitals or child caring institutions, proprietors of maternity hospitals or maternity

homes, and physicians and nurses responsible for the care of normal newborn and premature infants in general hospitals or child caring institutions, or maternity hospitals or maternity homes, to take all reasonable precautions to prevent the introduction and spread of diarrhea of the newborn, including the following

- a Formulae and other fluids offered to newborn infants in hospitals or child caring institutions, or in maternity hospitals or maternity homes shall be poured into individual feeding bottles at the time of preparation, and a nipple shall be attached to each bottle and covered with a cap. The entire product shall then be subjected to terminal heating by steam under pressure of not less than 15 pounds (121° Centigrade or 250° Fahrenheit) for not less than 5 minutes, or at a pressure of not less than 6 pounds (110°C or 230°F) for not less than 10 minutes, or by flowing steam at a temperature of not less than 100°C (212°F) for not less than 30 minutes. The temperature of the formula or fluid, as determined by periodic examination, shall be not less than 93°C (200°F) at the end of the heating process. The nipple cap shall remain on the bottle until the time of feeding. If fruit juices, or formulae containing lactic acid, meats, or cereals are given to newborn infants, they may be offered without such terminal heating, but shall be prepared with and stored in pre-sterilized equipment.
- b Normal newborn and premature infants born in a hospital or maternity hospital or maternity home shall not be kept in the same nursery, room or ward with sick infants or older children. Nurses giving care to infected patients shall not come in contact with infants in the normal newborn or premature infant nurseries. No infant born outside the hospital or maternity hospital or maternity home shall be admitted to the nursery for well infants, except after isolation for a period of one week. An infant born to a mother who has diarrheal or respiratory illness shall not be admitted to the nurseries for normal newborn or premature infants.
- c An infant suspected of having diarrhea of the newborn shall be promptly removed from the normal newborn or premature infant nurseries, and kept under isolation precautions. If, after observation, diarrhea of the newborn is found to exist, such infant shall then be transferred to an isolation nursery.
- d Individual equipment shall be provided for each infant except for the weighing scales, which shall be freshly covered for each infant. Common bathing and dressing tables are prohibited. The use of racks, carriers, or bassinet stands for holding or transporting more than one infant at a time is prohibited. Physicians and nurses shall wash their hands under running water before and after coming in contact with any infant.
- e Nursing care shall be given to each infant at the bedside. Space shall be adequate to give such care, provided that the total nursery floor space shall average not less than 24 square feet per infant, or the infants shall be placed in individual cubicles.
- f No room used as a nursery shall house more than 12 infants, nor shall such a room intercommunicate with other rooms used as nurseries. There shall be running hot and cold water for handwashing in each room used as a nursery, with the flow of water controlled by elbow, knee or foot valves. No nurse shall give care to more than 12 infants and their equipment.

Enacted January 16, 1948, to be effective January 1, 1949, except that the enforcement of either or both subdivisions "e" and "f" may be deferred for an individual institution for a period not later than January 1, 1951 by the State Commissioner of Health upon request of such institution.

The Massachusetts Committee on the Fetus and Newborn Infant, or its individual members, will welcome any opportunity to assist in planning for nursery construction or in giving informal advice regarding any problems concerning the health of newborn infants in the Commonwealth.

CLEMENT A. SMITH, M.D., *Chairman*

Boston

## BOOK REVIEW

*Diseases of Children* Edited by Donald Paterson, M.D. (Edin.), F.R.C.P., and Alan Moncrieff, M.D. (Lond.), F.R.C.P. Volume I, with contributions by twenty-nine authors. Fourth edition. 8°, cloth, 771 pp., with 154 illustrations. Baltimore: Williams and Wilkins Company, 1947. \$9.00.

This first volume of a standard treatise, first published in 1913 in a single volume, is the joint work of twenty-nine English specialists in their particular fields. The third edition was issued in 1934, and a new edition planned before the outbreak of World War II had to be abandoned because of hostilities and consequent difficulties. This fourth edition has been expanded into two volumes, and the text and illustrations thoroughly revised to bring them up to date. Sections have been added on the surgical aspects of congenital deformities, growth and development, the use of drugs in infancy and childhood, including the sulfonamides and penicillin, clinical pathology, acid-base regulation, anesthetics in the surgery of childhood, subdural hematoma in infancy, the treatment of megacolon, abdominal pain, surgery of the lung, treatment of pneumonia, diagnosis and treatment of collapse of the lung, and much new material on tuberculosis. The volume is divided into two parts, general considerations and diseases of children, including diseases and injuries of the newborn, diseases of nutrition, metabolism, the ductless glands, the digestive tract, the respiratory system, tuberculosis and allergy. Selected references are appended to each chapter. A good index concludes the volume. The book is well published. It is recommended for all medical libraries and should prove valuable to all physicians interested in pediatrics.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Approaches to Tumor Chemotherapy* A symposium of papers and discussions on various aspects of tumor chemotherapy, developed from the summer meetings of the Section on Chemistry (C) of the American Association for the Advancement of Science at Gibson Island, Maryland, 1945-1946. Edited by Forest Ray Moulton. 4°, cloth, 442 pp., illustrated. Washington: The Association, 1947. \$7.75.

Twenty-six main articles make up this special volume. Ninety-three specialists took part in the meetings in 1945 and 1946, and the main papers are included in this volume. The first part is a general review of cancer therapy. The second presents a series of papers on special methodology; the third, nutritional factors; the fourth, bacterial products; the fifth, nitrogen mustards; and the sixth, various clinical aspects. This series of papers reflects the current knowledge on the subject. The volume is well published in every way. It is recommended for all medical libraries, and should prove valuable to all physicians interested in tumors.

*Entwicklungsgeschichte des Krankheitsbegriffes* By Dr. Emanuel Berghoff. Second edition. 8°, cloth, 201 pp. Wien, Verlag Wilhelm Maudrich, 1947. \$5.00. *Wiener Beiträge zur Geschichte der Medizin* Vol. I. Distributed in the United States by Grune and Stratton, New York.

This monograph on the historical development of the ideas of disease discusses in order the significance of pre-Hippocratic ideas and the early theories of disease, Hippocrates and his school, Galen and the Middle Ages, the Renaissance and the seventeenth century, followed by chapters on animism and neuropathology, mesmerism and the Romantic school, the period of the end of the eighteenth and the beginning of the nineteenth centuries, the Vienna School, and cellular pathology and the bacteriologic era, serology and constitutional pathology. The work concludes with a chapter on the significance of social medicine in relation to disease ideas. The volume is concluded with a short list of references and an author index. An index of subjects would be appreciated in

a succeeding edition. The text is well arranged and well written. The type and paper are good and the printing is well done. The publication is up to the standard of prewar days. The monograph is recommended for all medical history collections.

*How Life is Handed On.* By Cyril Bibby M.A. M.Sc., F.L.S., senior lecturer, College of St. Mark and St. John, London. 8, cloth, 159 pp., with 62 illustrations. New York: Emerson Books Incorporated, 1947. \$2.00.

This small book is intended for the use of children and young adolescents. The text is written in so easy a style brought down to the educational level of the intended readers. The descriptions of the beginnings of life in animals and man are presented in a frank manner. There are additional chapters on the relation of the sexes, family life and adolescence as well as on the declining birth rate. The appendices contain a list of simple biologic experiments, books for further study and a glossary of terms used in the text. There is an index of plant and animal names and one of subjects. The author does not set any minimum limit on the age of children for which the book is intended, therefore it would be advisable for parents to pass on the book before giving it to their children. The printing, type and paper are good and the price is reasonable.

*Successful Dental Practice. Patient relations patient education—training planning—business principles.* By J. Lewis Blass, Ph.D. D.D.S., associate professor of periodontology, lecturer on practice management and lecturer on dental therapeutics, New York University College of Dentistry, and Irvin Tullin D.D.S. 8, cloth, 221 pp., with 42 illustrations, including 16 color plates. Philadelphia: J. B. Lippincott Company, 1947. \$6.00.

The authors write in detail on the management of patients, office management fees, insurance, legal matters and other problems that effect the business of a dental practice. The text is concluded with an atlas for patient education. A good index completes the volume. Valuable suggestions are presented for the improvement of the business side of practice, some of which could be of value to physicians, especially those relating to patient management. The volume is well published.

*Practical X-ray Treatment.* By Arthur W. Erskine M.D. Third edition revised and enlarged. 8, cloth, 155 pp. with 22 illustrations. Saint Paul: Bruce Publishing Company, 1947. \$4.50.

The first edition of this manual was published in 1931 and the second in 1936 and this revision of 1947 seeks to correct the mistakes made in the preceding editions. The text is devoted to the methods used by the author in the treatment of skin diseases, infections and inflammations, nonmalignant conditions, such as hyperthyroidism, hypertrophy of the tonsils, scrofula and fibroid tumors and cancer and malignant conditions. The first eight chapters deal with technique, dosage and effects on tissue. The chapter on scattering and distribution is illustrated with fourteen tables showing the back-scatter and distribution of x-rays of various degrees of quality under various physical conditions. The volume is well published in every way and should prove useful to physicians interested in the subject.

*Osteophthysis Pelvis et Femoris. Zugleich ein Beitrag zur Frage der spontanen Rückbildung malignanter Tumoren.* By Dr. Gottfried Hartmann, Assistent des pathol. anat. Institutes der Universität Wien. 8, cloth, 183 pp., with 19 illustrations. Wien: Verlag Maudrich, 1947. \$5.00. Distributed in the United States by Grune and Stratton, New York. *Wiener Beiträge zur Pathologie und pathologische Anatomie. Vol. I.*

This monograph on tuberculosis of the pelvis and femora is based on a complete study, clinical, roentgenologic, pathologic and histologic, of a fatal case in which both hips were involved. The patient was studied for a period of ten years. The histologic study of all tissues of the body after autopsy is comprehensive and is considered in the light of the question of spontaneous involution of malignant tumors. The text is divided into six parts: a short prologue followed by

the case history, a critical study of the histologic materials including an interpretation of the findings, the etiology and pathogenesis of the condition and its problems, and a summary. The text concludes with a list of references. An index would be appreciated. The publishing is well done in every way. The histologic plates are excellent. The monograph should be in all large medical libraries.

*La Médecine au Etats Unis de 1940 à 1946.* By Dr. Stanislas Lassalle in collaboration avec Dr. A. Gottschalk. 8, paper, 333 pp. Paris: Editions Hippocrate, 1946. 270 francs.

This volume consists of abstracts of the principal articles published in American medical periodicals during the period 1940-1946. Eighty-three different journals were consulted and the coverage is good. The emphasis is on therapeutics and clinical medicine. The subjects of gynecology, obstetrics, pediatrics, surgery and experimental medicine are also included. The abstract is well done and the book should prove valuable to French speaking physicians.

*Introducción al Estudio de la Plasmoterapia.* By Jose M. Masons de la Sección de farmacología del Instituto de Investigaciones Médicas de la Universidad de Barcelona. Prologo de Francisco Garcia Valdecasas. Catedrático de farmacología de la Facultad de Barcelona. 12, paper, 276 pp., with 15 illustrations. Barcelona: Editorial Miguel Serret, 1947.

This valuable monograph on the use of blood plasma is essentially a review of the world's literature through the year 1945. The author, after a chapter on history, discusses in order: physiopathology, hypoproteinemia and protidopenia, human and animal plasma and colloidal solutions, the indications of the use of plasma, the technique of its administration and the complications. The text is well organized and well written. The type and paper are excellent. Good indexes of authors and subjects conclude the volume. The monograph should be in all large medical libraries and should prove valuable to all persons interested in the subject.

*Headache.* By Louis G. Moench M.D., assistant clinical professor, University of Utah School of Medicine and internist, Salt Lake Clinic, Salt Lake City. 8, cloth, 207 pp., with 58 illustrations. Chicago: Year Book Publishers, Incorporated, 1947. \$3.50.

The researches of recent years have advanced greatly the knowledge of the troublesome symptom of headache. Dr. Moench has brought together in one volume for ready reference the latest ideas on the subject. He classifies the material according to the origin of the symptom: pathological anatomy and physiology followed by headache from intracranial disease, spinal puncture and ventriculography, cranial nerve neuralgias, headaches of ocular and nasal origin, from disease in the neck and from systemic disorders, histamine headaches, migraine, and headaches of emotional origin. A list of references is appended to each chapter, and a good index concludes the volume. The material is well organized. The printing is well done with a good type on good paper. The book is recommended for all medical libraries and should prove useful to the general practitioner for whom it is written.

*Neutron Effects on Animals.* By the staff of the Biochemical Research Foundation. Dr. Ellice McDonald, director, Newark, Delaware. 8, cloth, 198 pp. Baltimore: Williams and Wilkins Company, 1947. \$3.00.

The cyclotron employed in these researches was specially constructed for biochemical and biologic study. During an investigation on the blood for the Manhattan District it ran continuously for more than a year without missing a day. For the past eight years the staff of the Foundation has been studying the forces and material produced by the machine. The twenty papers presented in this volume represent the preliminary studies on the effects of neutrons on body tissues and fluids of the lower animals. The volume is well published in every way, and its price is reasonable. This is a book in a new field and is recommended for all medical libraries.



homes, and physicians and nurses responsible for the care of normal newborn and premature infants in general hospitals or child caring institutions, or maternity hospitals or maternity homes, to take all reasonable precautions to prevent the introduction and spread of diarrhea of the newborn, including the following

- a Formulae and other fluids offered to newborn infants in hospitals or child caring institutions, or in maternity hospitals or maternity homes shall be poured into individual feeding bottles at the time of preparation, and a nipple shall be attached to each bottle and covered with a cap. The entire product shall then be subjected to terminal heating by steam under pressure of not less than 15 pounds (121° Centigrade or 250° Fahrenheit) for not less than 5 minutes, or at a pressure of not less than 6 pounds (110°C or 230°F) for not less than 10 minutes, or by flowing steam at a temperature of not less than 100°C (212°F) for not less than 30 minutes. The temperature of the formula or fluid, as determined by periodic examination, shall be not less than 93°C (200°F) at the end of the heating process. The nipple cap shall remain on the bottle until the time of feeding. If fruit juices, or formulae containing lactic acid, meats, or cereals are given to newborn infants, they may be offered without such terminal heating, but shall be prepared with and stored in pre-sterilized equipment.
- b Normal newborn and premature infants born in a hospital or maternity hospital or maternity home shall not be kept in the same nursery, room or ward with sick infants or older children. Nurses giving care to infected patients shall not come in contact with infants in the normal newborn or premature infant nurseries. No infant born outside the hospital or maternity hospital or maternity home shall be admitted to the nursery for well infants, except after isolation for a period of one week. An infant born to a mother who has diarrheal or respiratory illness shall not be admitted to the nurseries for normal newborn or premature infants.
- c An infant suspected of having diarrhea of the newborn shall be promptly removed from the normal newborn or premature infant nurseries, and kept under isolation precautions. If, after observation, diarrhea of the newborn is found to exist, such infant shall then be transferred to an isolation nursery.
- d Individual equipment shall be provided for each infant except for the weighing scales, which shall be freshly covered for each infant. Common bathing and dressing tables are prohibited. The use of racks, carriers, or bassinet stands for holding or transporting more than one infant at a time is prohibited. Physicians and nurses shall wash their hands under running water before and after coming in contact with any infant.
- e Nursing care shall be given to each infant at the bedside. Space shall be adequate to give such care, provided that the total nursery floor space shall average not less than 24 square feet per infant, or the infants shall be placed in individual cubicles.
- f No room used as a nursery shall house more than 12 infants, nor shall such a room intercommunicate with other rooms used as nurseries. There shall be running hot and cold water for handwashing in each room used as a nursery, with the flow of water controlled by elbow, knee or foot valves. No nurse shall give care to more than 12 infants and their equipment.

Enacted January 16, 1948, to be effective January 1, 1949, except that the enforcement of either or both subdivisions "e" and "f" may be deferred for an individual institution for a period not later than January 1, 1951 by the State Commissioner of Health upon request of such institution.

The Massachusetts Committee on the Fetus and Newborn Infant, or its individual members, will welcome any opportunity to assist in planning for nursery construction or in giving informal advice regarding any problems concerning the health of newborn infants in the Commonwealth.

CLEMENT A SMITH, M D, *Chairman*  
Boston

## BOOK REVIEW

*Diseases of Children* Edited by Donald Paterson, M D (Edin), F R C P, and Alan Moncrieff, M D (Lond), F R C P. Volume I, with contributions by twenty-nine authors. Fourth edition. 8°, cloth, 771 pp., with 154 illustrations. Baltimore: Williams and Wilkins Company, 1947. \$9 00.

This first volume of a standard treatise, first published in 1913 in a single volume, is the joint work of twenty-nine English specialists in their particular fields. The third edition was issued in 1934, and a new edition planned before the outbreak of World War II had to be abandoned because of hostilities and consequent difficulties. This fourth edition has been expanded into two volumes, and the text and illustrations thoroughly revised to bring them up to date. Sections have been added on the surgical aspects of congenital deformities, growth and development, the use of drugs in infancy and childhood, including the sulfonamides and penicillin, clinical pathology, acid-base regulation, anesthetics in the surgery of childhood, subdural hematoma in infancy, the treatment of megacolon, abdominal pain, surgery of the lung, treatment of pneumonia, diagnosis and treatment of collapse of the lung, and much new material on tuberculosis. The volume is divided into two parts, general considerations and diseases of children, including diseases and injuries of the newborn, diseases of nutrition, metabolism, the ductless glands, the digestive tract, the respiratory system, tuberculosis and allergy. Selected references are appended to each chapter. A good index concludes the volume. The book is well published. It is recommended for all medical libraries and should prove valuable to all physicians interested in pediatrics.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Approaches to Tumor Chemotherapy* A symposium of papers and discussions on various aspects of tumor chemotherapy, developed from the summer meetings of the Section on Chemistry (C) of the American Association for the Advancement of Science at Gibson Island, Maryland, 1945-1946. Edited by Forest Ray Moulton. 4°, cloth, 442 pp., illustrated. Washington: The Association, 1947. \$7 75.

Twenty-six main articles make up this special volume. Ninety-three specialists took part in the meetings in 1945 and 1946, and the main papers are included in this volume. The first part is a general review of cancer therapy. The second presents a series of papers on special methodology, the third, nutritional factors, the fourth, bacterial products, the fifth, nitrogen mustards, and the sixth, various clinical aspects. This series of papers reflects the current knowledge on the subject. The volume is well published in every way. It is recommended for all medical libraries, and should prove valuable to all physicians interested in tumors.

*Entwicklungsgeschichte des Krankheitsbegriffes* By Dr Emanuel Berghoff. Second edition. 8°, cloth, 201 pp. Wien, Verlag Wilhelm Maudrich, 1947. \$5 00. *Wiener Beiträge zur Geschichte der Medizin* Vol I. Distributed in the United States by Grune and Stratton, New York.

This monograph on the historical development of the ideas of disease discusses in order the significance of pre-Hippocratic ideas and the early theories of disease, Hippocrates and his school, Galen and the Middle Ages, the Renaissance and the seventeenth century, followed by chapters on animism and neuropathology, mesmerism and the Romantic school, the period of the end of the eighteenth and the beginning of the nineteenth centuries, the Vienna School, and cellular pathology and the bacteriologic era, serology and constitutional pathology. The work concludes with a chapter on the significance of social medicine in relation to disease ideas. The volume is concluded with a short list of references and an author index. An index of subjects would be appreciated in

a succeeding edition. The text is well arranged and well written. The type and paper are good and the printing is well done. The publication is up to the standard of prewar days. The monograph is recommended for all medical history collections.

*How Life is Handled On*. By Cyril Bihby M.A., M.Sc., F.L.S. senior lecturer, College of St. Mark and St. Jobo, London. 8° cloth, 159 pp., with 62 illustrations. New York: Emerson Books Incorporated 1947. \$2.00.

This small book is intended for the use of children and young adolescents. The text is written in an easy style brought down to the educational level of the intended readers. The descriptions of the beginnings of life to animals and man are presented in a frank manner. There are additional chapters on the relation of the sexes, family life and adolescence as well as one on the declining birth rate. The appendices contain a list of simple biologic experiments, books for further study and a glossary of terms used in the text. There is an index of plant and animal names and one of subjects. The author does not set any minimum limit on the age of children for which the book is intended, therefore it would be advisable for parents to pass on the book before giving it to their children. The printing, type and paper are good and the price is reasonable.

*Successful Dental Practice. Patient relations patient education treatment planning-business principles*. By J. Lewis Blass Ph.D. D.D.S., associate professor of periodontology, lecturer on practice management and lecturer on dental therapeutics, New York University College of Dentistry and Irvin Tinklin, D.D.S. 8°, cloth, 221 pp., with 42 illustrations including 1 color plate. Philadelphia: J. B. Lippincott Company 1947. \$6.00.

The authors write in detail on the management of patients, office management, fees, insurance, legal matters and other problems that effect the business of a dental practice. The text is concluded with an atlas for patient education. A good index completes the volume. Valuable suggestions are presented for the improvement of the business side of practice, some of which could be of value to physicians especially those relating to patient management. The volume is well published.

*Practical X-ray Treatment*. By Arthur W. Ewings M.D. Third edition revised and enlarged. 8° cloth, 155 pp., with 22 illustrations. Saint Paul: Bruce Publishing Company, 1947. \$4.50.

The first edition of this manual was published in 1931 and the second in 1936, and this revision of 1947 seeks to correct the mistakes made in the preceding editions. The text is devoted to the methods used by the author in the treatment of skin diseases, infections and inflammations, nonmalignant conditions such as hyperthyroidism, hypertrophy of the tonsils, scrofula and fibroid tumors and cancer and malignant conditions. The first eight chapters deal with technique, dosage and effects on tissue. The chapter on scattering and distribution is illustrated with fourteen tables showing the back-scatter and distribution of x-rays of various degrees of quality under various physical conditions. The volume is well published in every way and should prove useful to physicians interested in the subject.

*Osteophthysis Pelvis et Femorum. Zugleich ein Beitrag zur Frage der spontanen Rückbildung malignanter Tumoren*. By Dr. Gottfried Hartmann, Assistent des pathol. anat. Institutes der Universität Wien. 8°, cloth, 183 pp., with 19 illustrations. Wien: Verlag Mandrich 1947. \$5.00. Distributed in the United States by Gruene and Stratton, New York. *Wiener Beiträge zur Pathologie und pathologische Anatomie*. Vol. I.

This monograph on tuberculosis of the pelvis and femora is based on a complete study, clinical, roentgenologic, pathologic and histologic, of a fatal case in which both hips were involved. The patient was studied for a period of ten years. The histologic study of all tissues of the body after autopsy is comprehensive and is considered in the light of the question of spontaneous involution of malignant tumors. The text is divided into six parts: a short prologue, followed by

the case history, a critical study of the histologic materials, including an interpretation of the findings, the etiology and pathogenesis of the condition and its problems and a summary. The text concludes with a list of references. An index would be appreciated. The publishing is well done in every way. The histologic plates are excellent. The monograph should be in all large medical libraries.

*La Médecine en Etats Unis de 1940 à 1946*. By Dr. Stanislas Lasalle, en collaboration avec le Dr. A. Gottschalk. 8° paper, 333 pp. Paris: Editions Hippocrate 1946. 270 francs.

This volume consists of abstracts of the principal articles published in American medical periodicals during the period 1940-1946. Eighty three different journals were consulted and the coverage is good. The emphasis is on therapeutics and clinical medicine. The subjects of gynecology, obstetrics, pediatrics, surgery and experimental medicine are also included. The abstract is well done, and the book should prove valuable to French speaking physicians.

*Introducción al Estudio de la Plasmoterapia*. By Jose M. Massons de la Sección de farmacología del Instituto de Investigaciones Médicas de la Universidad de Barcelona. Prologo de Francisco Garcia Valdecasas. Catedrático de farmacología de la Facultad de Barcelona. 12° paper, 276 pp., with 15 illustrations. Barcelona: Editorial Miguel Serret, 1947.

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*Morphologic Hematology* Special issue No 1 of *Blood, the Journal of Hematology* William Dameshek, M.D., editor-in-chief 4°, cloth, 200 pp New York Grune and Stratton, 1947 \$4.75

In this symposium twenty-six recognized authorities have combined in a discussion of the physiologic and pathologic morphology of the blood in man and in animals. The volume is well published in every way and should be in all medical libraries.

*Training in Clinical Psychology* Transactions of the first conference, March 27, 28, 1947, New York City 8°, paper, 88 pp New York Josiah Macy, Jr., Foundation \$1.50

This small volume presents the various papers read at the conference of specialists held in New York in 1947. The discussions centered on the problems of training in clinical psychology and psychoanalysis. The type, paper and printing are good, but the ring type of binding is not suitable for permanent preservation of valuable material. However, the volume should be in all medical libraries.

*Gifford's Textbook of Ophthalmology* By Francis H. Adler, M.D., professor of ophthalmology, University of Pennsylvania School of Medicine. Fourth edition 8°, cloth, 512 pp, with 310 illustrations Philadelphia W. B. Saunders Company, 1947 \$6.00

This standard textbook has been revised in the light of the original concept of Dr. Gifford. The book is intended primarily for medical students and general practitioners, with emphasis on conditions that they may safely treat themselves. The techniques of refraction and operations have been condensed considerably, and surgical procedures have been given a separate chapter. Special emphasis has been placed upon the relation of the eye to general medical and neurologic conditions. The references appended to each chapter have been confined to those in the English language. A good index concludes the volume. The text is well organized, and the publishing well done in every way. The book should prove useful to the general practitioner.

*Pharmacology, Therapeutics and Prescription Writing For students and practitioners* By Walter Arthur Bastedo, Ph.D., Ph.M. (Hon.), M.D., Sc.D. (Hon.), consulting physician, St. Luke's Hospital, New York, St. Vincent's Hospital, Staten Island and the Staten Island Hospital. Fifth edition 8°, cloth, 840 pp, with 82 illustrations Philadelphia W. B. Saunders Company, 1947 \$8.50

This new edition of a standard reference work first published in 1913 has been completely rewritten. This has been made necessary by the therapeutic advances since the printing of the previous edition in 1937. Parenteral administration is given due consideration. Material has been added on the amino acids, blood fractions, coagulants and anticoagulants, heparin, dicumarol, curarc, snake venoms, folic acid, rutin, thiouracil, sulfonamides, penicillin, streptomycin, demerol, metopon, the cardiac glycosides, the antimalarials, the mercury diuretics and the BAL treatment of poisoning by arsenic, gold and other substances. Details of the modern treatment of shock and of anemias, and syphilis are given. Carbon monoxide, carbon disulfide, the cyanides and lead are discussed, not as remedies but as serious poisons. A comprehensive index concludes the volume. The book is well published in every way, and a light paper is used, making a light volume for its size. It is recommended as a reference work for all medical libraries and for physicians.

*Edinburgh Post-Graduate Lectures in Medicine* Volume III 8°, cloth, 587 pp Edinburgh Oliver and Boyd, 1946 15 sh

This is the third of a series of volumes presenting in inexpensive editions the postgraduate lectures delivered in the Royal Infirmary of Edinburgh. This series comprises thirty lectures delivered during the season 1942-1943 by specialists and covers the whole field of medicine, including surgery. The volume is well published and should be in all medical libraries. It is an outstanding example of this type of publication.

*Fundamentals of Immunology* By William C. Boyd, M.D., associate professor of biochemistry, Boston University School of Medicine. Second edition 8°, cloth, 503 pp, with 50 illustrations and 66 tables New York Interscience Publishers, Incorporated, 1947 \$6.00

This textbook has been written primarily for students and research workers. First published in 1943, the book has been completely revised within the scope of its objective of presenting basic facts and not exhaustive discussions. Each chapter is documented with a list of references. The material is well organized, and the book is well published in every way and printed on a soft paper pleasing to the eye. It is an ideal textbook.

*Developmental Diagnosis Normal and abnormal child development clinical methods and pediatric complications* By Arnold Gesell, M.D., and Catherine S. Amatruda, M.D. Second edition, revised and enlarged 8°, cloth, 496 pp, with 21 illustrations New York Paul B. Hoeber, Incorporated, 1947 \$7.50

Dr. Gesell has thoroughly revised this new edition of his work, which was first published in 1941. A number of additional case studies have been incorporated in the text. They include diagnostic problems involved in amentia, convulsive disorders, cerebral injuries, blindness, deafness, infantile aphasia, congenital anomalies and prematurity. Material has been added on prenatal rubella, the Rh factor, retrolental fibroplasia and electroencephalography, as well as sections on behavior growth and hygiene of the fetal infant and on the physician's role in the problem of child adoption. The literature has been brought up to date. A good index completes the volume. The book is well published in every way. It is recommended for all medical libraries and should prove valuable to all physicians dealing with young children.

*Handbook of Diagnosis and Treatment of Venereal Diseases* By A. E. W. McLachlan, M.D., Ch.B. (Edin.), D.P.H., F.R.S. (Edin.), consultant in venereal diseases, City and County of Bristol, lecturer in venereal diseases, University of Bristol, and honorary consultant in venereal diseases, Bristol General Hospital. Third edition 12°, cloth, 375 pp, with 160 illustrations, 20 in color Baltimore Williams and Wilkins Company, 1947 \$5.00

The third edition of this British handbook has been revised to include the knowledge gained of the value of penicillin therapy. The soundness of the text is evidenced by the need of three editions in four years. The book reflects the best British opinions and experience. Manufactured in Great Britain, it is well printed with a good, large, legible type. Primarily intended for undergraduate and postgraduate students, it should prove useful to the general practitioner.

*Fundamentals of Psychiatry* By Edward A. Strecker, M.D., Sc.D., LL.D., Litt.D., professor of psychiatry and chairman of the department, Undergraduate and Graduate School of Medicine, University of Pennsylvania, psychiatrist to the Pennsylvania, Philadelphia and Germantown hospitals, consultant and chief-in-service, Institute of Pennsylvania Hospital, and consultant to the Surgeon General, United States Navy. Fourth edition 12°, cloth, 325 pp, with 21 illustrations Philadelphia J. B. Lippincott Company, 1947 \$4.00

This manual first published in 1942 has been thoroughly revised in this fourth edition. Much material has been added including a chapter on psychosomatic psychiatry. Two suggested nomenclatures have been included in the text. The soundness of the compend is evidenced by the demand for four editions since the publication of the first in 1942.

*Practical Clinical Psychiatry* By Edward A. Strecker, A.M., M.D., Sc.D., Litt.D., LL.D., professor of psychiatry, University of Pennsylvania, Franklin G. Ebaugh, A.B., M.D., professor of psychiatry, University of Colorado School of Medicine, and director, Colorado Psychopathic Hospital, and Jack R. Ewalt, M.D., professor of neuropsychiatry and director, Galveston State Psychopathic Hospital, University of Texas Medical Branch. Section on Psychopathologic

*Problems of Childhood* By Leo Kanner M.D. associate professor of psychiatry, Johns Hopkins University School of Medicine. Sixth edition. 8° cloth 476 pp with 35 illustrations and 12 tables. Philadelphia: Blakiston Company 1947. \$5.00.

This authoritative textbook first published in 1925 and last revised in 1940 has again been revised to the light of the extensive knowledge of psychiatry gained during the years of World War II. This edition includes both the military and standard nomenclatures. An extensive bibliography is appended to each main section and a good index concludes the volume. The book is well published in every way. It is recommended for all medical and mental libraries and to all physicians interested in psychiatry.

*Public Health Law* By James A. Tobey, Dr. P.H. 1.L.D. Third edition. 419 pp. New York: Commonwealth Fund 1947. \$4.50.

Much material has been added to this new edition of a standard reference monograph. Approximately two hundred and fifty new decisions of courts of last resort on various aspects of public health law have been referred to or abstracted; numerous alterations in governmental organization and administration have been noted and important legislative trends have been reported. The text is well printed with a good legible type on soft, light paper. A general index and one of cases conclude the volume. The book is recommended for all medical, public health and law libraries and should prove valuable to public health officers and lawyers.

*Communicable Diseases* By Franklin H. Top, M.D. M.P.H. medical director, Herman Kiefer Hospital, clinical professor of preventive medicine and public health, Wayne University College of Medicine and extramural lecturer on infectious diseases and epidemiology, School of Public Health, University of Michigan. Second edition. 8° cloth 992 pp with 95 illustrations and 13 color plates. St. Louis: C.V. Mosby Company 1947. \$8.50.

Dr. Top and his collaborators have revised all chapters of this standard work first published in 1941. Fourteen new chapters have been added on various diseases and the number of collaborators has been increased to twenty. The chapters on influenza, malaria and rickettsial diseases have been completely rewritten. Many illustrations in black and white and in color have been added. A bibliography is appended to each chapter. The appendices present morbidity tables and a glossary of medical words. A good index concludes the volume. The book is recommended for all medical libraries and to all physicians interested in communicable diseases.

*A Textbook of Clinical Neurology. With an introduction to the history of neurology.* By Israel S. Wechsler M.D. clinical professor of neurology, Columbia University neurologist, Mount Sinai Hospital and consulting neurologist, Montefiore Hospital and Rockland State Hospital, New York. Sixth edition. 8° cloth 829 pp with 162 illustrations. Philadelphia: W.B. Saunders Company 1947. \$8.50.

The first edition of this standard textbook was published in 1927 and the previous revision was made in 1943. This sixth edition has been revised to bring the text up to date. Material has been added and the chapter on psychometric tests has been completely rewritten and its name changed to Psychologic Diagnosis. The list of references attached to each chapter has been revised by the inclusion of new titles and the deletion of obsolete references. A comprehensive index concludes the volume. The book is well published in every way in the characteristic style of the publisher. It is recommended for all medical libraries and to all persons interested in neurology.

*The Rotunda Hospital 1745-1945* By O'Donell T.D. Browne M.B. M.A. M.A.O. (Univ. Dublin), F.R.C.P. (I), F.R.C.O.G. King's professor of midwifery, Trinity College, Dublin; gynecologist, Sir Patrick Dun's Monksdown and Stewarts Hospitals, Dublin. 4° cloth 296 pp with 44 plates and a chart. Baltimore: Williams and Wilkins Company 1947. \$11.00.

In this volume is portrayed the history of the Rotunda Hospital of Dublin, Ireland. The book is divided into six

parts. The first two are devoted to a chronologic history of this famous obstetric hospital and the Dublin School of Midwifery. The succeeding chapters discuss the struggle against puerperal fever, operative midwifery, anesthesia, gynecology and eclampsia. In the section on puerperal fever the part Oliver Wendell Holmes of Boston played in the prevention of this disease is fairly and impartially discussed. The volume is well published in every way. It is printed with a good large type of soft paper. The book should be in all medical history collections.

*Endocrinology of Neoplastic Diseases. A symposium by eighteen authors.* 8° cloth 392 pp. New York: Oxford University Press 1947. \$11.00.

This symposium, originally published in *Surveys* in 1944, has been revised and brought up to date as of 1946. The various papers discuss the endocrinologic aspects of tumors of the pituitary body, ovary, uterus, breast, prostate, testicle, adrenal glands, thyroid and parathyroid glands, pineal gland and the pancreas and present the latest information on the various topics. A long bibliography is appended to each chapter. The printing is well done with a good type set on a half-filled paper not essential for this type of book. The price seems excessive for the volume. The work is recommended as a reference text for medical libraries and should prove valuable to physicians interested in the subject.

*Clinical Pediatrics* By I. Newton Kugelmann M.D. Ph.D. S.D. attending pediatrician, Downtown Hospital, Pan American Clinic, Lynn Memorial Hospital, Monmouth Memorial Hospital and Muhlenberg Hospital, New Jersey. Second edition. 8° cloth 409 pp. New York: Oxford University Press 1947. \$4.00.


The purpose of this epitome is to emphasize the determining features of pediatric problems as a basis for more detailed study of the individual child in health and disease. The material is arranged to an outline manner and divided into eighteen parts based on an anatomic classification. The volume is well printed and should prove useful to physicians interested in pediatrics and should be valuable in differential diagnosis.

*Essentials of Pharmacology* By Frances K. Oldham M.Sc. Ph.D. research associate in pharmacology, University of Chicago; F.L. Kelsey, Ph.D. associate professor of pharmacology, University of Chicago; and E.M. K. Gelling, Ph.D., M.D. Frank P. Hixon Distinguished Service Professor and chairman of the Department of Pharmacology, University of Chicago. 8° cloth 440 pp. Philadelphia: J.B. Lippincott Company 1947. \$5.00.

This manual is intended as an introductory text in pharmacology in which the general principles of the subject are stressed. The text is divided into three parts: general principles, functional drugs and chemotherapeutic agents. To each chapter is appended a selected list of references for further reading. A good index concludes the volume. The text printed on a good soft paper should prove useful to students and others desiring a good compendium of the subject.

*Endogenous Endocrinology: Including the causal cure of cancer compendium.* By Dr. Jules Samuels. 8° cloth 539 pp with 30 illustrations. Amsterdam: Holland-Holdert and Company 1947. \$10.00.

The author is contemplating the publication of a large five-volume treatise on endogenous endocrinology and is issuing this volume as a preliminary compendium to his treatise. He outlines his theory of hypophyseal dysfunction and of its relation to various diseases. He believes that restoration of the balance of the pituitary gland may arrest tumor growth. He claims that after his method of treatment a number of patients have survived for five to seven years and have continued to enjoy good health. The first part of the book discusses the subject in general and the use of the short wave current to treatment. The second part considers the various diseases susceptible to treatment, with a long section on proliferation diseases including cancer. The book is well printed on good paper but is unduly bulky for its size. All physicians interested in cancer should have access to this volume.



This baby's mother learned  
about Mead's Oleum Percomor-  
phum from her physician, not from  
public advertising or displays  
"Servamus Fidem"

## HOW much sun does the infant really get?

*Not very much* (1) When the baby is bun-  
dled to protect against weather or (2) when  
shaded to protect against glare or (3) when  
the sun does not shine for days at a time  
Mead's Oleum Percomorphum is a pro-  
phylactic against rickets available 365½  
days in the year, in measurable potency and  
in controllable dosage *Use the sun, too.*

Mead Johnson & Co., Evansville, Ind., U.S.A.

# The New England Journal of Medicine

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Volume 238

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Number 15

## PRESIDENTIAL ADDRESS\*

THOMAS H. LANMAN, M.D.†

BOSTON

WHETHER we like it or not, the social and economic problems of medicine today must be faced, and by constructive efforts we must attempt their solution. As physicians, we are prone to keep away from politics and perhaps properly so. At least, we have not to any degree played politics" in the usually accepted sense of the word. I believe that the time has come when this society should take a more active part as a society, in the solution of these urgent problems. However much we may do as individuals, I believe that we do not use to full advantage the collective experience and ideas of the members of the society, who represent so well the art and science of surgery in New England. I believe that the recommendations of this society on such vexing problems as nursing service, hospital administration, costs of surgical care and training of surgeons can and should carry a greater weight. We are in a strategic position, for we represent, as no similar group does a cross-section of New England as a whole. We are familiar with the complexities of these problems in many widely differing localities.

These problems cannot be solved by an attempt to apply to New England as a whole the ideas that may emanate from one central body of the United States. Just as certainly, we cannot apply with good effect the methods of solution in northern New England that may be effective in meeting the needs of greater Boston. The remedies must be based on the needs of the local community, and the local conditions are known best by those who live in that community. The mere knowledge of the local needs, however, is not enough. These needs must be integrated with the over-all picture.

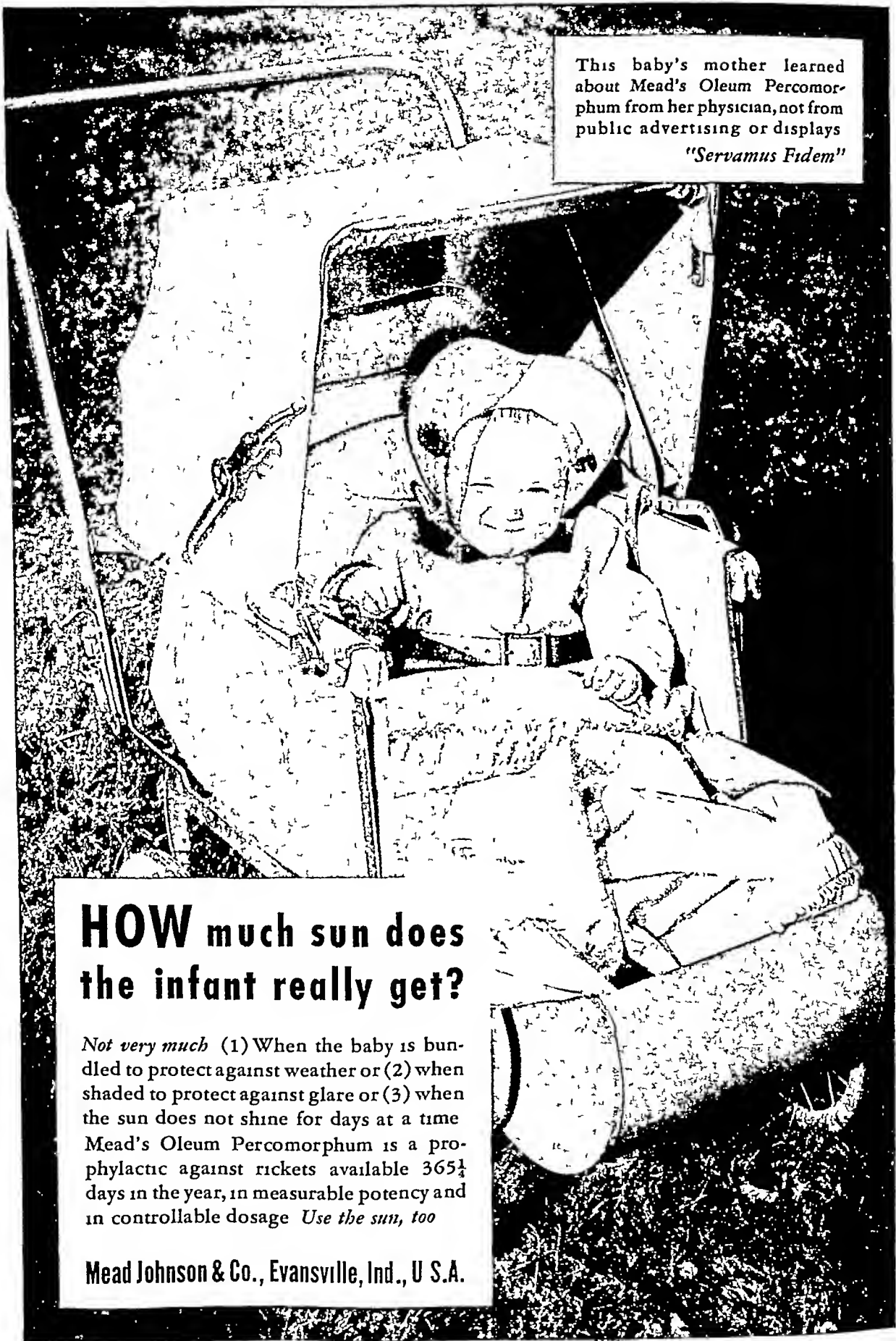
A commander-in-chief must have a sound, tactical and strategic plan, which must be carried out by the division, battalion or even company commander. The methods of putting the plan into effect, however, by commanders of the lower echelons must be co-ordinated with the over all campaign, or

chaos will result. I do not know which is worse, a good plan coming from a centralized headquarters that does not permit of variation to meet the local needs or a good local plan that takes little or no account of the problem as a whole throughout the country.

The New England Surgical Society is particularly well equipped to do constructive thinking and co-ordinate local with general plans. In surgical training for example, other urgent questions such as the nursing situation, the changing problems in hospital administration and, in particular, professional fees and the cost of surgical illness are important, and we must take our part in solving them. But the training of surgeons is a large enough subject to warrant its being considered alone although any solution must include consideration of the others—notably, the costs of surgical illness. In the New England States, as perhaps in no other part of the country of comparable geographical size, we have many, if not all of the conditions that affect the training of a surgeon and his later surgical career and we have a cross section of this subject as it applies to the country as a whole. We have a large metropolitan area, Boston, which has not one but three Class A medical schools, all of which are endeavoring to meet this problem—the training of the surgeon. In New Haven, Burlington and Hanover are single medical schools, and the problems in these localities may be quite different in their practical solution. We have our larger industrial centers, and we have our smaller urban communities and our rural districts. The combined individual opinion of members of this society, therefore, should carry great weight. We cannot solve the problems by meeting the needs of the teaching centers alone. By the same token, what is applicable to Bridgeport or Salem may not be suitable for Bangor or St. Albans, nor can the needs of the rural communities be met by methods applicable to the cities, whether or not they have medical schools. I believe that the rules of the American Board of Surgery must be made more flexible and that they should be influenced by the

† Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 1, 1947.  
† Full scale professor of 1918, Harvard Medical School, Surgeon, Children's Hospital.





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## PRESIDENTIAL ADDRESS\*

THOMAS H. LANMAN, M.D.†

BOSTON

WHETHER we like it or not, the social and economic problems of medicine today must be faced, and by constructive efforts we must attempt their solution. As physicians, we are prone to keep away from politics and perhaps properly so. At least, we have not to any degree played politics in the usually accepted sense of the word. I believe that the time has come when this society should take a more active part, as a society, in the solution of these urgent problems. However much we may do as individuals, I believe that we do not use to full advantage the collective experience and ideas of the members of the society who represent so well the art and science of surgery in New England. I believe that the recommendations of this society on such vexing problems as nursing service, hospital administration, costs of surgical care and training of surgeons can and should carry a greater weight. We are in a strategic position for we represent, as no similar group does, a cross-section of New England as a whole. We are familiar with the complexities of these problems in many widely differing localities.

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† Chief, Department of Surgery, Harvard Medical School, Surgeon, Children's Hospital.



sound and collective opinion of the members of this society. We should furnish our representatives on the various boards with a clearer picture of the varying needs in the various communities.

This year, the Program Committee is devoting a larger part of its attention to papers that deal with the broader aspects of surgery. It is our hope to find out, if possible, what this society might do as a society in further advancing the purpose of various agencies, political and medical, that have been organized on a national basis. Our members have had a prominent part in the organization and the aims of the American Board of Surgery. Our members have also played an important part in the American College of Surgeons, the National Cancer Society and similar groups. I think it should continue to do so and should make its considered opinions as a society heard and felt in the recommendations of these bodies. Already, conditions are quite different, as far as the surgical training program is concerned, than they were when the Board of Surgery was organized. The war and its political, social and economic sequelae have disrupted surgical training to a considerable degree. In addition, the practice of surgery is going through tremendous advances and changes—I use the two words purposely, for I do not consider *all* the present changes advances.

It is certain that the minimum requirements before a candidate can be certified by the American Board of Surgery are sound in principle, but I believe they need a greater flexibility in their application. How many of our members meet the present requirements of the American Board of Surgery, as far as their formal training in length of internships and residencies is concerned? I know that I do not.

In his address as president of the American Orthopedic Society, in June, 1946, Dr J. Albert Key,<sup>1</sup> of St. Louis, stated

Due to the unswerving devotion to duty of the Membership Committees, our American Orthopedic Association comprises a group of orthopedic surgeons whose ability cannot be questioned, and yet, I doubt if 10 per cent of our present membership could meet the present training requirements. It is thus evident that it must be possible for one to become proficient in orthopedic surgery by other routes. I wonder if we are not making a grave mistake in our attempt to regiment the training of orthopedic surgery. To limit future orthopedic surgeons to those of our young medical graduates who can be forced into a mold is to exclude many whose qualifications justly entitle them to certification and whose abilities as orthopedic surgeons would be of great value.

This statement from one of the leading orthopedic surgeons in America is significant, and it is equally significant in its application to the training of the general surgeon. (Although there is some difference of opinion regarding the relative importance of the surgeon and the orthopedist, there is no question that both should be well trained.) We have only to read the list of members of this society to appreciate that many competent, out-

standing surgeons have reached the enviable positions that they hold without going through the present formal requirements of the American Board of Surgery. No one should misinterpret these remarks and feel that I, in any way, advocate lowering the ideals for the training of a surgeon. But I do agree with Dr. Key that we are in danger by regimentation, of excluding from certification many men whose talents and abilities justify such recognition as surgeons.

The following paragraph of a letter (recently published in the *New England Journal of Medicine*, from a young surgeon now in the course of receiving his training in Boston for the American Board of Surgery is quoted as being of interest:

As the ward beds are encroached on by private and semi-private cases, there will be fewer and fewer cases under the care of the house staff. Coincidentally, and stimulated by the requirements of the American College of Surgeons and American Board of Surgery, more and more men desire a longer training period. Thus, the problem of adequate training for the young surgeon becomes increasingly difficult. No one will deny that increased training is a desirable thing, but where are the beds to train so many for so long? That would be difficult to answer in any event, but with the increasing shortage of ward beds it will become even more so. The answer to these questions must be forthcoming soon.

As this young correspondent points out, the so-called "ward beds" in the teaching hospitals are becoming fewer because of certain insurance plans such as the Blue Cross, as well as other economic factors. As a result, the opportunities for the proper surgical training of residents—particularly the actual operative work done by the house staff—are proportionately poorer. In passing, it is rather interesting to note his phraseology, "ward beds are encroached on by private cases." This is certainly a different point of view from that held by those of us who were trained in the era when a private patient was unheard of in the institutions in which we served as interns.

Another side of this question will become apparent to the young surgeon when he completes his training, and I quote in substance the editorial reply to the letter referred to:

There will be a further problem confronting the young surgeons who have completed their residencies in these institutions where, under excellent supervision by the chief, 80 to 90 per cent of the ward patients are properly cared for by the house staff, but who, unfortunately for themselves and for the communities in which they are needed, elect to remain in the large teaching hospitals as junior attending surgeons. In such institutions, these men are placed on service for periods of several months during the year, but if they are fair to the resident staff, by "handing down" the bulk of the operative work (as others did for them when they were of the house staff) they get little return in practical operative

experience from the amount of time that they devote to the hospital. On the other hand, the young surgeon who has had four or five years of active, well supervised training may fare little better if he goes to a community hospital, unless he is fortunate or wise enough to choose a locality in which there is real need for a surgeon.

These trends appear to be inevitable, and it is certain that the present system of postgraduate surgical training does not suffice and, what is of even greater importance in my opinion, it has now a tendency to disrupt an equitable distribution of surgeons. Too few opportunities are available for the present requirements in postgraduate surgical training, furthermore, too many well trained young surgeons remain in the large teaching centers, partly because little incentive is offered for moving to smaller communities. There are several ways of relieving this situation, in particular, a more widespread adoption of the fellowship or preceptorship as a method of surgical training is desirable, and with this, the development of community hospitals as teaching centers. It is here that our society can be of great assistance. Other schemes will undoubtedly be devised as the necessity arises. Certainly, efforts should be made to meet the demand not only for providing the necessary number of well trained surgeons but also for their equitable distribution throughout the country.

I suggest that some method be devised whereby the collective opinion of members of this society be more accurately obtained and that our recommendations be, in some way, officially brought to the attention of the governing bodies of societies of national scope. This year, we have a paper by Dr Harvey about the American Board of Surgery. We shall also hear something of the surgical problems in smaller communities, and a report on "detection clinics" in their statewide and national scope. All these have a bearing on the present problems. It may be worth while for our executive committee to consider having even more time devoted each year to a discussion of these questions, and to accomplish this it might be desirable to have

a longer annual meeting. Another suggestion is to have a second meeting during the year at which such problems could be discussed, leaving the purely scientific papers for the annual meeting. One hesitates to suggest the formation of still another committee, but perhaps this is the best way to study these problems adequately. Surely they are important enough to justify active and practical steps to forward their solution. Concerning the problem of the training of surgeons, I suggest that although certification or some similar tangible recognition of the adequacy of a man's training is desirable, the requirements must be flexible enough to meet the varying needs of a representative geographical area such as New England. Rules for certification that are too rigid may defeat their purpose. In addition, it should not be forgotten that whereas an examination may cover the tangible technical ability of the candidate, even though he passes with honor, he may be a dangerous man in his community if he does not possess the intangible qualities of character that cannot be determined by examination alone. These intangibles are better apparent to those who know the candidate by personal contact. It is here that the preceptorship has its unique advantage, and I suggest that this society is in a strong position to encourage its wider use and to know how far such preceptorships can be usefully employed to meet the varying needs of New England — not only for Board certification but also as a means of attracting men of high caliber to practice surgery where they are needed. Above all this society should make every effort both to provide adequate training for men of good character and to see that these men have adequate opportunities to practice where they are most needed. Today, an equitable distribution of well trained surgeons is even more important than their number.

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## ROENTGENOGRAPHIC STUDIES OF THE GASTROINTESTINAL TRACT FOLLOWING SECTION OF THE VAGUS NERVES FOR PEPTIC ULCER\*

MAX RITVO, M D,† AND IRVING A SHAUFFER, M D ‡

BOSTON

THERE is widespread interest in the surgical treatment of chronic, intractable peptic ulcer by section of the vagus nerves. Dragstedt and his co-workers<sup>1</sup> in Chicago were the first to employ the procedure systematically, and since their publication of the results of supradiaphragmatic vagus resection in 2 patients in 1943 they have reported progressively larger series of cases, which reached a total of 90 in 1946.<sup>1,2</sup> Moore<sup>3</sup> has recorded 40 cases. Grimson and Ruffin<sup>4-6</sup> have discussed a series of 57 cases. Previous reports of the findings in transthoracic, bilateral vagus-nerve resection have described changes in size, shape, motility and emptying of the stomach following operation. The findings have varied in different series and from time to time in the same series. Carlson,<sup>7</sup> in 1923, noted that bilateral vagotomy resulted in decrease of tone and diminution in the number of hunger pangs although the gastric contractions remained apparently normal in amplitude. In 1926 McCrea<sup>8</sup> stated that the motor activity of the stomach was not altered by unilateral vagotomy and, except for a decrease in initial emptying time, was not appreciably influenced by section of both vagus nerves. Hartzel,<sup>9</sup> in experimental work with dogs in 1929, demonstrated that section of both vagus nerves decreased the acidity of the gastric contents. In addition he noted a marked increase in initial and a slight increase in final emptying time of the stomach with no gastric dilatation. On post-mortem examinations of 2 dogs, seven and thirty-five days, respectively, after vagotomy, he found no abnormalities in the stomach. In 1935 Ferguson<sup>10</sup> described decreased gastric tone and delayed initial emptying time after sectioning the vagi of 10 monkeys. An interesting feature of this work was that cardiospasm occurred postoperatively in all the animals whether the vagi were sectioned in the cervical region or transabdominally. In 1938 Winkelstein and Berg,<sup>11</sup> who found that anterior vagotomy and partial gastrectomy produced achlorhydria, advocated anterior subphrenic vagotomy with gastroenterostomy for duodenal ulcers to prevent the development of jejunal ulcer. Weinstein et al.,<sup>12</sup> in a comprehensive review of the literature in 1944, came to the conclusion that vagotomy was only partially successful in the treatment of peptic ulcer, since delay in emptying of the stomach was the sole result achieved. In a series of 15 cases

Dragstedt<sup>13</sup> indicated that 3 required subsequent gastroenterostomy after vagotomy because of obstruction and delayed gastric emptying. One patient developed acute dilatation of the stomach eight weeks postoperatively, and 2 had gastric atony during the first week or two after operation. In the remaining cases peristalsis, position and tonus of the stomach appeared to be normal, and the esophagus and intestines revealed no abnormalities on roentgenographic study.<sup>14</sup> Later observations by this group<sup>15,16</sup> showed that there was a decrease of gastric tonus subsequent to the surgery. By using balloons, they found that hunger contractions remained normal in duration but were diminished in amplitude. Although decreased gastric motility was found in all cases, no decrease occurred in intestinal motility.

Moore and his associates<sup>17</sup> described definite changes in gastric function after vagus resection. There was delay in the initial emptying and prolongation of final emptying. The former was considered to be normally one half to one and a half minutes, and the latter about two and a half hours. By the use of electronic apparatus, the authors found postoperative absence of large gastric contractions and decrease in peristaltic activity. Eight months postoperatively they noted a return to normal in the amplitude of gastric contraction but a persistence of abnormality of pattern. In a later paper Moore<sup>18</sup> stated that gastric emptying returned to normal after six to eight months, with disappearance of all motility changes in that time. Subsequently, he<sup>3</sup> noted that gastric motility approached normal levels at the end of a year. The gastric atony observed roentgenoscopically disappeared in three to nine months, although delay in emptying persisted in some cases. Changes distal to the pylorus were indefinite and variable. Baronofsky et al.,<sup>19</sup> in 1946, found marked atony and dilatation of the stomach after vagus resection. Grimson and Ruffin<sup>4,5</sup> reported a series of 28 patients in 1946 and described marked delay in emptying, moderate dilatation of the stomach and markedly decreased or absent peristalsis. If gastroenterostomy or gastric resection had been performed previously, the above changes did not occur. Six hour residues of 90 to 100 per cent were present in 10 cases, with lesser degrees of delay in emptying in 10 others. Seven of the remaining 8 patients had had previous gastric operations. Three cases required operation because of retention, and the stomach appeared to empty well after sev-

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eral months. Later, Smith, Ruffin and Baylin<sup>8</sup> reported a series of 50 cases in which, after operation, there was moderate or marked dilatation of the stomach, with absent or slow, arrhythmical peristalsis. Objective healing of peptic ulcers occurred in several weeks or a few months. Observations after three to twenty-seven months revealed that in no case had the stomach returned

with chronic peptic ulcer have been performed at the Boston City Hospital. Thirty were men, and 3 women. The ages ranged from twenty-one to fifty-seven, 4 patients being twenty-one to thirty, 9 thirty-one to forty, 8 forty-one to fifty, and 2 fifty-one to fifty-seven years of age. Twenty-one patients had had no gastric surgery prior to the vagus resection. Three had had previous gastro-

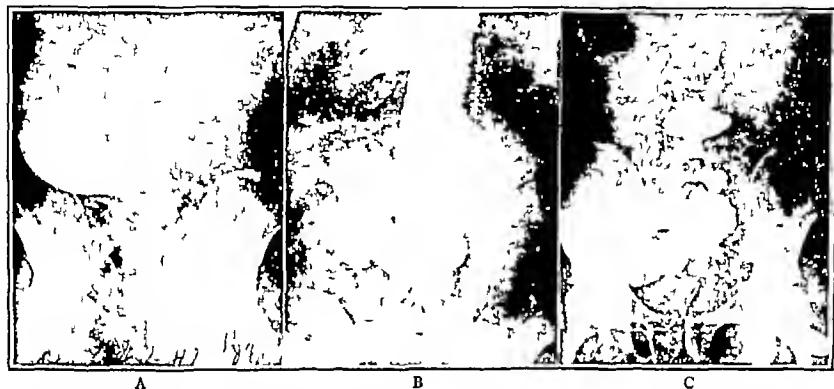


FIGURE 1 Roentgenograms in a Fifty-Five Year Old Man with a History of Duodenal Ulcer of Twenty Years Duration and with Pain That Had Become Intractable to Diet and Other Forms of Medical Therapy After Laparotomy. He Was Entirely Relieved of All Complaints and Was Able to Be on a Normal Diet without Recurrence of Symptoms.

A demonstrates the appearance of the stomach ten days after vagotomy. A roentgenogram taken six hours after the ingestion of an opaque meal shows the stomach to be markedly dilated and atonic with absent peristalsis and with retention of the entire opaque meal in the stomach. Twenty-four-hour observation showed marked enlargement and atonicity of the stomach with about 50 per cent gastric residue, and at forty-eight hours there was approximately 50 per cent retention in the stomach. B shows that the stomach, four months after vagotomy, was normal in size and atonic with very sluggish peristalsis — the film taken about fifteen minutes after the ingestion of the opaque meal shows the duodenum contracted and irregular in outline with small amounts of the opaque material in the upper loops of jejunum, indicating that emptying of the stomach is taking place. C which demonstrates a roentgenogram taken six hours after that illustrated in B, shows only a small amount of the opaque meal remaining in the stomach. The head of the opaque column is in the terminal ileum, indicating slight hypomotility and the small bowel loops are slightly atonic but otherwise not remarkable.

to normal. Although the changes were less marked in most cases, the increased dilatation and absence of peristalsis persisted in some.

Grimson and his co-workers<sup>20</sup> reported 57 cases in July, 1947, and made the comment that temporary difficulty in swallowing was noted in 20. In 26 patients studied for small-bowel changes, transit through the jejunum was delayed, the caliber usually increased slightly, and the mucosal pattern tended to become coarse. A new phase of investigation must be considered in the work of Machella,<sup>21</sup> Smith, Ruffin and Baylin<sup>8</sup> and Grimson et al.<sup>20</sup> These studies consisted in the use of urecholine (urethane B-methyl choline) to stimulate peristalsis and increase the rate of emptying of the stomach after vagotomy. The effect of the drug persisted for thirty to forty-five minutes.

#### MATERIAL AND METHOD

Since December 1, 1945, bilateral supradiaphragmatic resections of the vagus nerves on 33 patients

enterostomies with persistence of ulcer symptoms. Of 5 patients who had had partial gastrectomies, 3 had developed intractable marginal ulcers, and 2 refractory jejunal ulcers slightly distal to the stoma. In the 21 patients who had had neither gastrectomy nor gastroenterostomy, 20 had chronic duodenal ulcers, with histories of perforation or hemorrhage in some. One of these, a thirty-five-year-old woman, presented an ulcer of the lesser curvature of the stomach.

Each of the patients in our series was examined roentgenographically and fluoroscopically prior to the resection of the vagus nerves and one or more times postoperatively (Fig 1-3). After the operation, roentgenographic studies were made as soon as it was deemed advisable clinically or when the patient was willing to report to the x-ray department. Thirteen patients were first re-examined within one to three weeks after operation, 16 in three to eight weeks, 3 within ten to fourteen weeks, and 1 after twenty-eight weeks had elapsed.

Of these, 6 have not returned for subsequent observations. Re-examinations were carried out at intervals of a few weeks or months in the remainder of this group, the number and frequency of the studies being determined principally by the patient's co-operation in returning despite the fact that all were symptom free. Several were unwilling to lose time from work or were unco-operative for other personal reasons. Twelve of the group were studied twice, 10 were observed three times, 4 returned four times, and 1 was examined on five occasions. One case has been followed for fourteen months,

bowel, but since no significant changes in caliber or mucosal pattern were demonstrated, this practice was discontinued.

#### PATIENTS WITH NO PREVIOUS GASTRIC OPERATION

The first group to be considered comprised 21 patients who had had neither gastrectomy nor gastroenterostomy previously. Fourteen were examined within three weeks after the vagus resections had been performed, all showed dilatation and atonicity of the stomach. In 5 cases the stomach was markedly dilated, 8 patients presented gastric

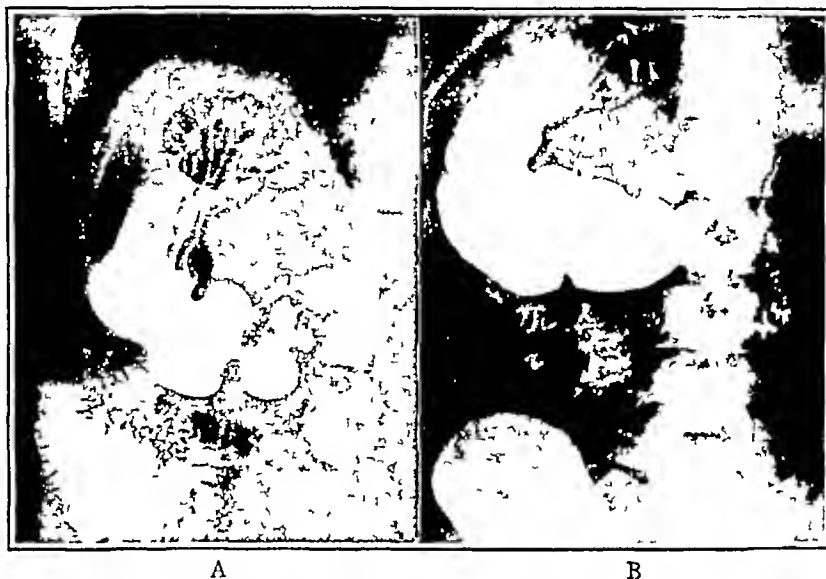


FIGURE 2 *Roentgenograms in a Thirty-Five-Year-Old Woman with a History of Ulcer of Four Years' Duration Whose Response to Medical Therapy Had Been Very Unsatisfactory. After Vagotomy, She Was Promptly Relieved of All Symptoms. Roentgenographic Observations Were Continued at Intervals for Almost a Year and Showed the Stomach to Be Slightly Dilated and Atonic, with Sluggishness or Absence of Peristalsis and Slight Delay in Emptying. There has Been No Recurrence of Pain.*

A, roentgenogram taken before operation, shows the stomach to be hypertonic, with vigorous peristalsis and moderate pylorospasm, the duodenal bulb is markedly irregular and presents an ulcer-crater formation, and there is tenderness over it on fluoroscopic palpation. B, roentgenogram taken twenty-two weeks after vagotomy, demonstrates that the stomach is atonic, with sluggish peristalsis and a widened pylorus, the duodenal bulb shows moderate distention, a constriction across its proximal portion and no ulcer crater or tenderness on fluoroscopic palpation (barium was present in the upper jejunum soon after the ingestion of the opaque meal, and there was no gastric residue at six hours).

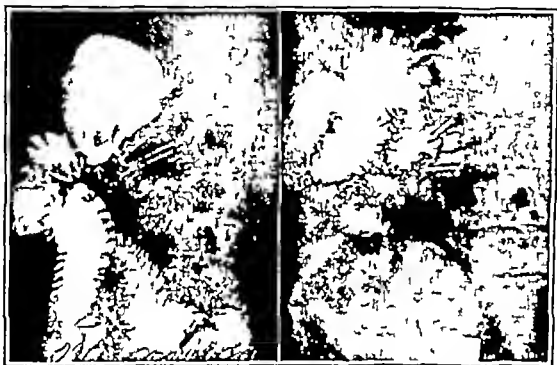
3 for eleven months, 5 for seven to ten months, 10 for four to six months, and the remainder for less than four months postoperatively. In each case the esophagus, stomach and duodenum were studied with the barium meal, followed by routine six-hour and twenty-four-hour roentgenograms to determine motility and stasis. If a residue was present in the stomach at the twenty-four-hour observation, the patient was again seen at forty-eight hours and at seventy-two hours or until the stomach was empty. In the first few cases observations were made at hourly intervals after the ingestion of the opaque meal for study of the small

dilatation and atonicity of a lesser degree with enlargement to about twice the normal size. Another showed only slight dilatation. Six patients presented shallow, sluggish, ineffective and arrhythmic peristalsis, in 2 cases there was complete absence of peristalsis. All these patients had retained secretions in the stomach at the time of fluoroscopic study. Fourteen patients showed marked delay in both initial and final gastric emptying. Three had no evidence of any emptying of the opaque material after six hours. Seven had 80 to 95 per cent six-hour gastric residues, and in 4 cases there was 20 to 50 per cent six-hour retention. The marked

delay in the final emptying time is further illustrated by the fact that at the end of twenty-four hours 100 per cent gastric residue was observed in 1 case, 80 per cent in 1, 50 to 60 per cent in 2 and 5 to 15 per cent in 3—a total of 7 cases with twenty-four-hour stasis. At forty-eight hours 1 patient had 80 per cent gastric retention, and another showed 60 per cent gastric residue. The former had a gastroenterostomy performed soon afterward. In 5 cases the initial postoperative examinations were made within three to six weeks after operation. The stomach was dilated to twice the normal size in 3 and was normal in size in 2. All 5 presented sluggish, arrhythmical peristalsis. In this group

showed shallow, sluggish peristalsis, in the other peristalsis was normal. One had no six-hour residue, the second had a trace of the opaque meal retained at six hours, and the last showed 20 per cent gastric residue at the end of three hours.

Seven patients were examined five to six months after operation. In 1 the stomach was normal in size. 4 were found to have only slight dilatation, and in 2 the stomachs were about twice the normal size. Peristalsis was normal in 3 cases and was shallow, sluggish and arrhythmical in the remainder. Gastric residue of approximately 10 per cent at the end of six hours was noted in 5 cases and 25 per cent in 1 case, no six-hour film was



A

B

FIGURE 3 Roentgenograms in a Fifty-One Year-Old Man with a Long History of Recurrent Duodenal Ulcer. Eleven Years Previously He Had Had an Operation after an Acute Perforation Because of Severe Pain. Partial Gastrectomy Was Performed Five Years Later. Until Vagotomy He Had Recurrent Attacks of Pain and Required Hospitalization on Numerous Occasions.

A roentgenogram taken three weeks prior to vagotomy shows a functioning gastrojejunostomy with a large ulcer crater (arrow) in the jejunum in the region of the anastomosis. B roentgenogram taken twenty-one weeks after vagotomy shows that the ulcer crater is no longer demonstrable and that the remaining portion of the stomach is atonic and slightly dilated. Gastric emptying proceeding normally; there was no tenderness over the stoma or the upper jejunal loops, and the patient was free of symptoms and has continued to feel well.

2 patients had 50 to 55 per cent six-hour gastric residues, 1 had 15 per cent residue, and the stomach of 1 was empty at six hours. The fifth patient was not checked at the end of six hours, but after three hours the stomach was about 60 per cent empty. Two patients could not be examined postoperatively until three or four months after operation.

One patient was followed for a month, at the end of which the stomach was twice the normal size, with deep, slow and arrhythmical peristalsis and with a gastric residue of about 80 per cent at the end of six hours. Three patients were observed three to four months after the operation. The stomachs were slightly increased in size. Two

obtained in 1. In 5 patients the initial emptying showed less delay than that immediately after operation but was nevertheless considerably prolonged. In 2 cases the initial emptying was unchanged, being increased as immediately postoperatively. Two patients, seven to eight months after operation, showed stomachs of normal size with sluggish peristalsis. One of these had a 20 per cent six-hour gastric residue, the other had no retention.

In 1 case after an interval of fourteen months the stomach was slightly dilated, with peristalsis of good quality and a six-hour gastric residue of 5 per cent. After eleven months a second patient

presented a stomach that was dilated and atonic, peristalsis was deep and sluggish, and 45 per cent gastric retention was found at the end of six hours. The dilatation and gastric retention appeared to be due to marked constriction of the duodenal bulb. Of the 4 patients in this group whose postoperative roentgenographic findings are not described above, 1 died of a cervical-cord tumor, 1 had had a gastroenterostomy performed at another hospital, 1 has not returned, and the fourth had a subsequent gastroenterostomy, which is discussed below.

#### PATIENTS WITH PREVIOUS GASTROENTEROSTOMY

There were 3 patients who had had gastroenterostomies prior to vagus resection. When studied after the vagotomy, there was slight dilatation of the stomach. One case examined three months postoperatively showed good gastric tone, normal peristalsis and 5 per cent gastric residue at the end of six hours. Another was re-examined one month and three months after the operation and presented similar findings, with 5 per cent gastric stasis at the end of six hours. The third had an unusual progression: the first postoperative examination, after eight months, showed 100 per cent gastric residue at six hours and 50 per cent at twenty-four hours. He returned two months later, when there was complete emptying of the stomach in three hours. He failed to report for further examinations, stating that he had no complaints and did not wish to lose time from work. At both examinations the stomach was slightly dilated, and peristalsis was very sluggish. The gastroenterostomy was not functioning at either observation. As mentioned above, 1 patient had a gastroenterostomy after resection of the vagus nerves because of marked gastric dilatation and retention. Roentgenographic examination five months after this operation revealed 5 per cent gastric residue in the portion of the stomach distal to the stoma. Gastric tone was good, and there was prompt emptying via the stoma.

#### PATIENTS WITH PREVIOUS PARTIAL GASTRECTOMIES

There were 5 patients who had partial gastrectomies and subsequently developed intractable marginal or jejunal ulcers. In each of these the initial postoperative roentgenographic examination was made one to five weeks after operation. All showed dilatation of the stomach, with retained secretions and 10 to 15 per cent gastric residue at six hours. No evidence of ulcer crater was found, nor was there tenderness on fluoroscopic palpation in any of these cases postoperatively. One patient in this group after ten months had a 10 per cent gastric residue, although the greater portion of the stomach had been resected. Five months later 2 patients presented 5 per cent gastric residue and

no dilatation of the stomach. Two at the end of two to three months showed the remaining portion of the stomach still slightly dilated, there was no six-hour residue in 1 case, and 5 per cent in the other. In 1 patient a gastrocolic fistula was found after the vagus resection. Despite an ileosigmoidostomy the fistula persisted when he was last examined three months after the vagus resection.

#### PATIENTS WITH TRANSABDOMINAL VAGUS RESECTION

Also included in our series are 4 cases in which vagus resection had been performed transabdominally. Two patients had partial gastrectomies at that time, 1 had no operation on the stomach, and the last had had a previous partial gastrectomy and subsequently developed a jejunal ulcer. Four weeks after vagotomy, the patient who had had no other operation showed no gastric dilatation, peristalsis was shallow, sluggish and arrhythmical, and there was 40 per cent gastric residue in six hours. At the end of six weeks 1 patient who had had a gastric resection at the time of the vagotomy showed slight dilatation of the gastric remnant, with retained secretions. There was a 5 per cent residue at the end of six hours. The other who had had gastric resection at the time of the vagus section showed no dilatation of the gastric remnant at the end of two months. There was retained secretion in the stomach at the time of the examination, but no six-hour residue was found. The fourth patient, a thirty-year-old man who had had a previous gastric resection with a subsequent jejunal ulcer, was examined one and a half weeks after operation. The esophagus was not remarkable, the gastric remnant was markedly dilated and filled with secretions, and the efferent jejunal loop was dilated. No tenderness was present on fluoroscopic palpation. There was 30 per cent gastric residue at six hours. As he complained of regurgitation, vomiting, and distress, re-examination was carried out a week later. At that time the esophagus presented changes consistent with cardiospasm, with narrowing at the esophageal hiatus, reverse peristalsis and marked delay in the passage of thin and thick barium mixture. The esophageal constriction did not cause complete obstruction, the opaque material gradually entering the stomach in a small stream. Re-examination a week later showed similar changes. The patient was esophagoscoped shortly afterward and was found to have no demonstrable narrowing at the junction of the esophagus and stomach, the instrument passing without difficulty. The condition improved, and he was soon able to swallow without dysphagia. Carlson, in discussing a paper by Grimson,<sup>4</sup> reported the development of temporary esophageal stenosis in 1 case subsequent to trans-thoracic vagus-nerve resection. Similar esophageal change has been reported in Ferguson's<sup>10</sup> study of 10 monkeys. Grimson et al., in July, 1947, reported

difficulty in swallowing observed in 20 cases after supradiaphragmatic vagotomy

#### FURTHER OBSERVATIONS

Tenderness was not present on fluoroscopic palpation, and no ulcer crater was demonstrable postoperatively. The duodenal bulb was not clearly visualized in the early roentgenographic examinations in several cases. This was due to marked delay in the initial emptying time. The duodenal cap in patients with chronic duodenal ulcers showed gradual dilatation and decrease in spasticity within a few weeks in some cases. Gastric stomal and jejunal ulcers disappeared shortly after operation. The small bowel was not remarkable in size or mucosal pattern, the motility was slow, apparently owing to delay in initial gastric emptying because as the emptying time decreased, the motility became normal.

#### SUMMARY

A group of 29 patients with transthoracic section of the vagus nerves and 4 with transabdominal vagus-nerve resection were studied roentgenographically. In the early postoperative stages there was definite gastric dilatation and atonicity in most cases. Sluggish, ineffective and arrhythmical peristalsis or absent peristalsis was associated with the dilatation and atonicity. Emptying times both initial and final, were markedly increased. These changes occurred to a lesser degree in patients with previous gastroenterostomies and in those with partial gastrectomies. Two patients had gastroenterostomies after the vagotomy for dilatation and retention.

Follow-up studies showed a return toward the normal in the above changes within six months to a year. Complete return to normal in all respects was not found in any case, 1 patient having been followed for fourteen months after the operation.

The ulcers healed promptly after operation. This was especially striking in the cases of stomal and jejunal ulcers in the patients with partial gastrectomy.

The postoperative size of the small bowel was not remarkable in any case, the motility was slow

apparently owing to the delay in emptying of the stomach.

One patient developed temporary dysphagia after transabdominal vagus-nerve resection.

We are indebted to Dr William R. Morrison, surgeon in chief, First Surgical Service, Boston City Hospital for his assistance and co-operation in the collection and preparation of the material for this paper.

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## MULTIPLE LOCALIZED PLEURAL EFFUSIONS AS A MANIFESTATION OF CONGESTIVE HEART FAILURE\*

### Report of a Case

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**E**FFUSION into the general pleural cavity is a frequent manifestation of congestive heart failure. On the other hand, pleural effusion localized in an interlobar space is not a common finding, since only 15 cases have been recorded in the literature.<sup>1-11</sup> Multiple, localized pleural effusions associated with heart failure are apparently even more unusual since no record of this phenomenon has been found in a careful review of the available literature.

Although the case reported below is quite similar, in most respects, to those already reported with a single pleural effusion localized in an interlobar space in congestive heart failure, the multiple effusions encountered are of particular interest and appear to justify a report.

#### CASE REPORT

S McD, a 39-year-old, single man, was admitted to the hospital on December 4, 1946, complaining of swelling of the ankles, cough and shortness of breath. The patient stated that he had been well until 2 months before admission, when he had first noticed swelling of the ankles. This condition continued more or less unchanged until admission. About 1 month before admission he developed a continuous cough, productive of moderate amounts of whitish sputum. At the same time he became increasingly short of breath, and this symptom was aggravated by exertion. Two weeks before admission the abdomen began to swell, the cough became distressing, and the shortness of breath became more marked. Because of the progressive nature of the symptoms he was referred to the hospital.

The patient was said to have had rheumatic fever at 13 years of age, but the details of this illness were not known. However, he had never had any cardiac symptoms. There was nothing in the history to indicate a previous episode of congestive heart failure. In February, 1942, he had been admitted to the hospital because of a fractured patella. At that time, in addition to the injury to the knee, physical examination revealed a blood pressure of 140/80, cardiac enlargement, a marked thrill over the entire precordium, a loud presystolic murmur over the apex and a booming systolic murmur over the aortic area. The lungs and abdomen were normal, and there was no peripheral edema.

In 1942 the patient had been rejected for service in the Army because of heart trouble.

He gave no history of pneumonia or tuberculosis. He had had gonorrhea in early adult life. No history of syphilis was obtained. He had drunk large quantities of beer and whisky during the war years.

The family history was irrelevant.

Physical examination revealed a thin, confused man, who was moderately dyspneic, with slight cyanosis of the lips. He coughed frequently, producing a moderate amount of whitish, frothy sputum. The body weight was 68 kilograms (150 pounds). He was 69 inches in height. The skin was pale and moist from perspiration, it was not icteric. The

veins of the head and neck were markedly engorged and tortuous. The pupils were small, round and regular, the reacted normally to light and accommodation. Examination of the fundi was within normal limits. The trachea was in the midline, and there was no tug. The left anterior portion of the chest was more prominent than the corresponding region on the right. The percussion note over the entire chest was normal. Loud, moist, bubbling rales were audible throughout both lung fields, anteriorly and posteriorly. No thrills or shocks were palpated over the precordium. On percussion the relative area of cardiac dullness was found to be increased, extending approximately 12.0 cm to the left of the midsternal line in the sixth intercostal space and 5 cm. to the right in the fourth intercostal space. The rhythm of the heart was totally irregular. Auscultation was not entirely satisfactory at the time of admission because of the many extraneous noises in the chest. However, when the chest cleared somewhat a loud systolic murmur could be heard at the apex, and both systolic and diastolic murmurs could be heard at the base over the aortic area and along the left sternal border. The liver was enlarged and slightly tender, the edge was easily felt approximately 10 cm. below the costal margin in the midclavicular line. The spleen was not palpable. Shifting dullness was present in both flanks. There was pitting edema of the chest and abdominal walls as well as massive, pitting edema of the hips, scrotum, penis, thighs, legs, ankles and feet. There was no clubbing of the fingers or toes. There was no lymph-node enlargement.

The temperature was 98.6°F, and the respirations 26. The heart rate at the apex was 100 and at the radial artery was 88 per minute, a pulse deficit of 12 beats per minute. There was no capillary pulse. The blood pressure was 130/80.

Examination of the blood disclosed a red-cell count of 4,200,000, with a hemoglobin of 13.2 gm per 100 cc., and a white-cell count of 7200, with 69 per cent neutrophils, 26 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. The urine gave a + test for albumin and the specific gravity was 1.026. The sediment showed occasional red and white cells. The test for sugar was negative. Urobilinogen determination on a freshly voided single specimen was over 2 mg per 100 cc. The blood urea nitrogen was 15 mg, the blood glucose 74 mg, the plasma cholesterol 156 mg, and the total protein 5.2 gm per 100 cc, the icteric index was 9.5. The blood Hinton test was negative.

An electrocardiogram taken on the day after admission showed the heart action to be grossly irregular because of auricular fibrillation. Right-axis deviation was present (four tracings in 1939 had shown a normal sinus rhythm).

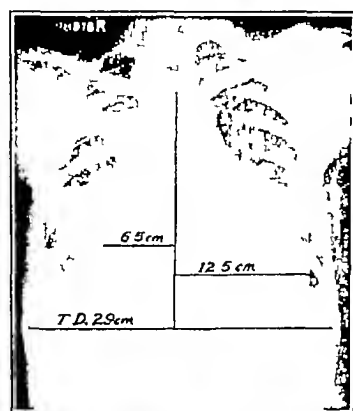
A routine teleroentgenogram of the chest (Fig 1) taken on admission showed the heart to be considerably enlarged, measuring 19 cm in its transverse diameter—an increase of 50 per cent over the average for the patient's height and weight. The area of the cardiac shadow was 235.0 sq cm. Both lungs showed moderate congestive changes and edema, particularly on the right. The right costophrenic sulcus was obliterated, probably owing to a small amount of fluid or to old adhesive pleurisy. However, the striking feature of the chest film was a well defined, circular shadow on the right side at the level of the eighth posterior interspace in the region of the transverse (horizontal) interlobar space (Fig 1 A and B). It measured approximately 6 cm in its greatest diameter. Further examination of the x-ray film revealed two additional unusual shadows, one of which had a double contour and was located along the right upper lateral portion of the chest wall (Fig 1 A and B), the other was centrally located at the level of the arch of the aorta and was obscured for the most part by the spine. This shadow was

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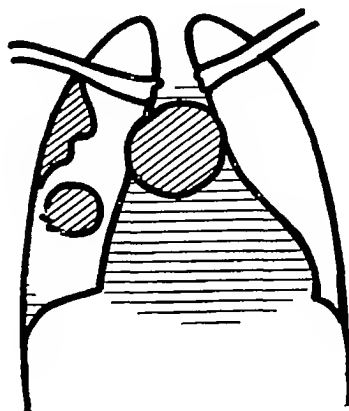
best visualized in its entirety in the upper anterior portion of the chest in the lateral view (Fig. 1 *A*, *B*, *C* and *D*). It was circular in outline and measured approximately 6 cm. in diameter.

The patient was put to bed and was given supportive treatment. He was completely digitalized within 48 hours. At

remained irregular. He received ammonium chloride for 3 days and on the 4th hospital day he was given 1 cc. of mercupurin intravenously with an unsatisfactory diuresis. On December 8 he was given intravenous infusions of glucose in water because of dehydration of the tongue and mucous membranes. This resulted in an impressive diuresis and an



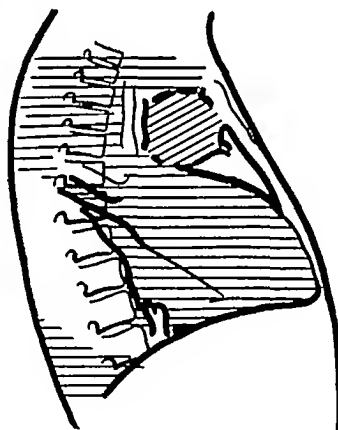
A



B



C



D

FIGURE 1

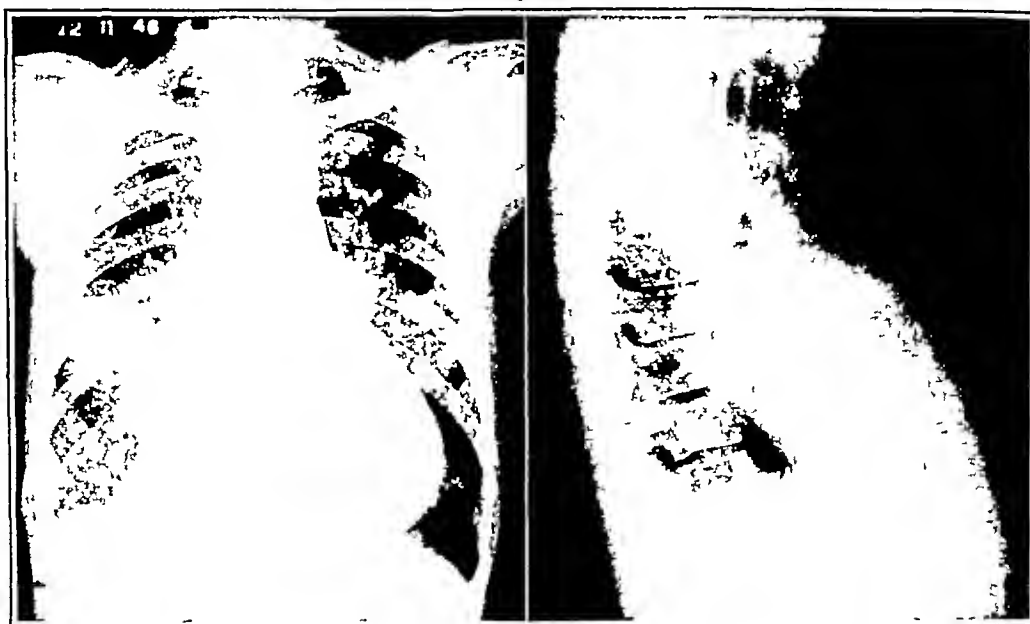
*A* is an anteroposterior roentgenogram of the chest taken on admission (December 4 1946) showing the usual shadows representing multiple localized pleural effusions the pulmonary congestion and the enlarged heart. *B* is a diagrammatic representation of *A*. *C* is a right lateral roentgenogram taken on the same day showing the large circular shadow (arrows) representing a localized pleural effusion in the anterior superior paramediastinal space. *D* is a diagrammatic representation of *C*.

the end of that time he appeared somewhat improved but there was little or no change in the edema. He was maintained on 0.1 mg. of digitoxin daily. The lungs showed some clearing but he continued to have a distressing cough productive of considerable amounts of frothy sputum. The apical heart rate was 72 per minute and the cardiac rhythm

obviously decreased in peripheral edema. The weight at that time was 58 kilograms (128 pounds), a loss of 10 kilograms (22 pounds) in the first 6 days of the hospital stay. On the 8th hospital day a second roentgenogram of the chest (Fig. 2) showed a definite decrease in the transverse diameter of the heart from 19 cm. to 17.5 cm. and also considerable clear-

ing of the congestive changes in the lungs. The area of the cardiac shadow was 217.0 sq cm. The shadow in the region of the transverse interlobar fissure and the shadow along

the head and neck, were no longer engorged. All evidence of edema had completely disappeared. The lungs revealed only a few rhonchi and some scattered rales. The patient



A

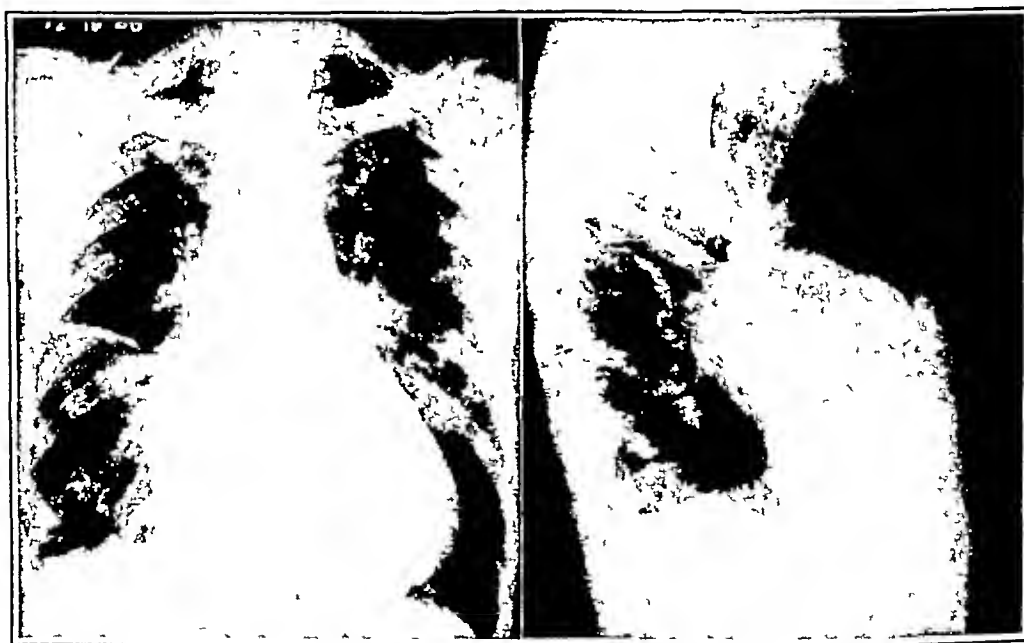
FIGURE 2

B

*A is an anteroposterior roentgenogram of the chest taken on December 11, 1946, showing a decrease in the size of the interlobar effusion and in the loculation of fluid in the right upper lateral chest wall, it also shows a decrease in the diameter of the aortic arch and the cardiac shadow. B is a right lateral roentgenogram taken on the same day, showing that the loculated effusion in the anterior, superior mediastinal space had completely disappeared.*

the right upper lateral portion of the chest wall had decreased considerably in size. The centrally located shadow along the upper anterior portion of the chest wall directly

weighed 54.5 kilograms (120 pounds). Auscultation of the heart was as previously noted. The blood pressure was 110/70. A repeat electrocardiogram continued to show auricular



A

FIGURE 3

B

*A is an anteroposterior roentgenogram taken on December 19, 1946, showing further improvement in the lung fields and in the size of the heart; the interlobar effusion appears as a narrow fusiform band. B is a right lateral roentgenogram taken on the same day.*

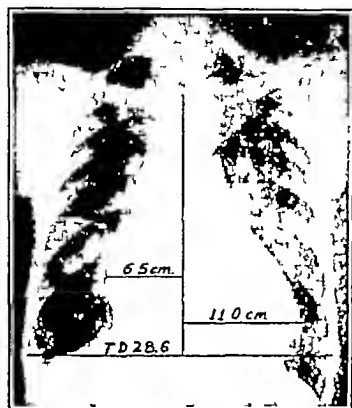
under the manubrium of the sternum had disappeared completely as the lateral chest film (Fig 2 B) showed. By the 9th hospital day marked improvement was evident. The veins of

fibrillation but no essential change from the previous tracing. The heart rate at the apex was 78 beats per minute. The liver had decreased considerably in size, and at that

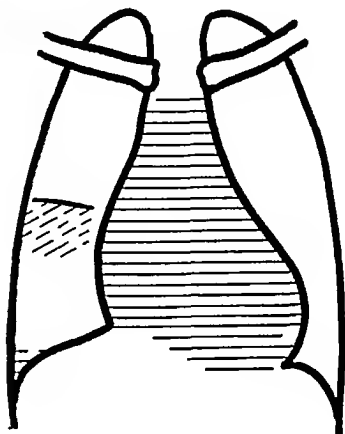
time its edge was measured approximately 5 cm below the costal margin in the midclavicular line. The spleen was not palpable and the shifting dullness in the flanks had disappeared. Sixteen days after admission a repeat roentgenogram of the chest (Fig. 3A) demonstrated a slight decrease in the transverse diameter of the heart and further clear

The shadow in the right upper lateral portion of the chest was no longer present. A lateral film of the chest taken at the same time disclosed progressive improvement consistent with the changes noted in the anteroposterior view (Fig. 3B).

During the following 12 days the steady improvement continued on a maintenance dose of digitoxin. All signs of heart



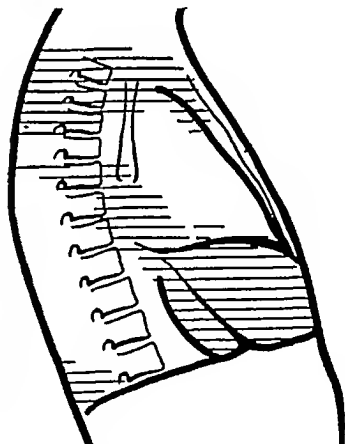
A



B



C



D

FIGURE 4

A is an anteroposterior roentgenogram taken on January 11, 1947, eighteen days after discharge showing that the original interlobar effusion had reduced to a narrow line (the other localized pleural effusions were gone). B is a diagrammatic representation of A. C is a right lateral roentgenogram taken on the same day, showing the middle lobe of the right lung well outlined by the remnants of the effusion in the interlobar space. D is a diagrammatic representation of C.

ing of the congestive changes in the lungs. The area of the cardiac shadow at that time was 210 sq. cm., a reduction of 25 sq. cm., or 10.6 per cent, from that of the original area. The large circular shadow in the region of the interlobar fissure reported in the original film (Fig. 1) showed a marked reduction in size and now appeared as a narrow fusiform band measuring approximately 5 cm. long and 0.7 cm. wide.

failure had disappeared. The weight averaged 54.5 kilograms (120 pounds). The temperature remained normal throughout the hospital stay. The patient was discharged improved 20 days after admission.

Eighteen days after discharge, a follow up roentgenogram of the chest (Fig. 4A and B) showed continued improvement. The original shadow was represented by a narrow line

A lateral chest film taken at the same time revealed the middle lobe of the right lung well outlined by the remnants of the effusion in the interlobar space (Fig 4 C and D)

### DISCUSSION

The patient was admitted as an ordinary case of rheumatic heart disease with a severe degree of congestive heart failure. Apparently, this was his first episode of failure. Routine anteroposterior and lateral roentgenograms of the chest taken on admission revealed the unusual shadows described. On admission there was some question of their origin. Although localized interlobar effusions are most commonly of pneumonic or tuberculous origin<sup>7, 12</sup> the negative history of a pulmonary infection and the absence of fever were against either localized collections of empyema or pulmonary tuberculosis with localized areas of pleurisy with effusion. The absence of chest pain, hemoptysis, and thrombosis of the peripheral venous system was evidence against the diagnosis of multiple infarctions of the lung. The striking clinical improvement that followed ordinary therapeutic measures (bed rest, digitoxin and diuretics) and the simultaneous regression of the shadows immediately ruled out the possibility of primary or metastatic carcinoma and obviously made multiple, localized pleural effusions as a manifestation of heart failure the most probable diagnosis.<sup>13</sup> Of interest was the absence of physical signs over the areas noted in the roentgenograms. Naturally no attempt was made to aspirate these areas.

In the previously reported cases of interlobar effusion associated with heart failure in which post-mortem examinations were done<sup>3, 5, 8</sup> either local adhesions or adhesive pleurisy with obliteration of the entire pleural cavity with the exception of the small space between the lobes of the lungs was found. This resulted in the accumulation of serous fluid within the free space. A study of these cases indicates that the transverse interlobar space is the most common site of interlobar effusions. On the other hand the evidence suggests that effusion in the long or oblique fissure is unusual and that multiple, localized pleural effusions as a manifestation of congestive heart failure are extremely rare.

The location of the loculations of fluid in the case presented was interesting. Repeated roentgenograms of the chest revealed beyond question that the circular shadow in the right middle-lung field was in the transverse interlobar fissure.

It may be assumed that the shadow along the right upper lateral area of the chest wall was due to a loculation of serous fluid in an area in the pleural cavity where no adhesions were present between the visceral and parietal pleura.

The shadow centrally located in the anterior portion of the chest at the level of the arch of the aorta was of particular interest, not only because of its location but also because it was the first of the

shadows to disappear. It was believed that this shadow was due to a loculated serous effusion in the anterior superior paramediastinal space.

Schwedel<sup>13</sup> makes the statement that interlobar effusions are characteristically the first to disappear after an effective diuresis or digitalization, or both. He attributes this rapid disappearance either to the small amount of fluid that is usually present in an interlobar space or to the fact that the fluid is enveloped by two visceral pleural surfaces, each of which might promote more adequate absorption than the parietal pleura. However, the rapid disappearance of the anterosuperior paramediastinal effusion and the loculation of fluid in the right upper lateral portion of the chest wall long before the disappearance of the interlobar effusion indicates that there may be exceptions to the sequence described in his statement.

As in many cases of interlobar effusion studied, no antecedent history of an inflammatory reaction of the pleura or pneumonia could be obtained. Although pleural reactions are common in repeated episodes of congestive heart failure one is hardly justified in using this explanation in the case reported above, since this was the patient's first bout of decompensation.

### SUMMARY

A case illustrating multiple, localized pleural effusions as a manifestation of congestive heart failure is presented.

That these findings are somewhat unusual in heart failure is indicated by the fact that no record of a similar case has been found in the literature.

I am indebted to Dr. Lawrence A. Martineau, director of the Department of Roentgenology, Rhode Island Hospital, for his co-operation in this study.

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## THE INEFFECTIVENESS OF ALUMINUM SUBACETATE IN RHEUMATOID ARTHRITIS\*

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**ENCOURAGING** results from the use of aluminum salts in the treatment of 12 patients with rheumatoid arthritis, active and inactive, were reported by Helfet.<sup>1</sup> In an effort to evaluate this therapy we employed aluminum salts according to his method for the treatment of a comparable series of patients with this disease. This report presents our results.

Helfet predicated the use of aluminum salts in rheumatoid arthritis upon certain theoretical premises, which are briefly summarized as follows: The first of these was that, regardless of the etiology, the symptoms of rheumatoid arthritis are the outcome of a secondary or physiologic hyperparathyroidism, he regarded the clinical features of rheumatoid arthritis as in many ways analogous to those of hyperparathyroidism. The second was the theory that parathormone is primarily concerned with the regulation of phosphorus metabolism exercised by control of the blood inorganic phosphate level.

Helfet proposed and tried the use of aluminum salts in rheumatoid arthritis according to the foregoing postulates from which he deduced the following rationale. Since the major fault in the disease according to his reasoning, lies in an overproduction of parathormone with its attendant decalcification of the bones, removal of the stimulus responsible for hypersecretion of the hormone — the blood inorganic phosphate level — should be the effective point of attack. Reduction of the blood phosphate level may be accomplished by a low phosphorus intake in the diet, but such a diet is impractical. An alternative procedure is the administration of aluminum salts orally. These combine with phosphate in the bowel, and the resulting precipitate of insoluble aluminum phosphate is excreted unchanged. The absorption of phosphate is thereby diminished, and the blood phosphate level held down. Less parathormone is then secreted, he reasoned, and in turn less calcium is drained from the skeleton.

A discussion of the pros and cons of Helfet's speculative concepts of the etiology of rheumatoid arthritis, or of parathyroid function, and the influence of aluminum salts is beyond the scope of this paper. We have been interested in the use of aluminum therapy primarily to evaluate its empirical value in rheumatoid arthritis.

Helfet administered to his patients 4 cc of a 2.5 per cent solution of the aluminum salt (either aluminum acetate or aluminum gluconate) four times daily. All patients, in addition, received at least a pint of milk daily to prevent the possible development of rickets from overdosage of aluminum salts. No toxic reactions were noted. Constipation, when present, was easily controlled with mineral oil.

With this regime alone, and without adjuvant therapy of any sort, marked clinical improvement was reported. Of 15 patients, including 12 cases of rheumatoid arthritis and 3 of ankylosing spondylitis, 12 improved in color, 10 increased in weight, and 9 described great relief from joint pain. Only 2 were unimproved. The response of the patients was manifested within three or four weeks by a sense of well-being, improved complexion, appetite and energy as the outstanding benefits. Increased motion was noted in all articulations except those previously ankylosed. In some cases the spindle-shaped swelling of the finger joints disappeared.

## METHODS

Twelve patients with rheumatoid arthritis in different stages of the disease comprised our series. Study of a group as large as Helfet's was initiated for comparison of results to determine whether further investigation of aluminum therapy in a large series of patients was warranted. Patients in this program did not receive any other treatment. Simple analgesics and local physical therapy were permitted when discomfort was severe.

Patients were classified as presenting the early, moderate advanced or terminal stage according to the severity of the signs.<sup>2</sup> The rheumatoid status was designated as active or inactive. The latter showed definite osteoporosis in addition to other clinical features to serve as objective guides to response to this treatment. Of the 12 cases 4 were early, 4 others moderate, and another 4 were advanced. Prior to the start of therapy 8 of the 12 cases were active, and 4 were inactive.

All patients received 4 cc of a 2 per cent solution of aluminum acetate four times daily in addition to a quart of milk daily. This treatment was sometimes supplemented by periodic placebo injections of isotonic saline solution to avoid any prejudice in the minds of those expecting the customary "injections for arthritis" given to many of the other patients in the clinic.

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Radiographic studies and determinations of the erythrocyte sedimentation rate and blood calcium, phosphorus and phosphatase were performed periodically

All patients were followed for from one to two years. Evaluation of the response to treatment was carried out by means of the criteria provided in our therapeutic score card<sup>3</sup>

### RESULTS

Of the 12 patients observed under aluminum salt therapy, 1 showed great improvement, and another, slight improvement, the status of the others was unchanged. In the objective evaluation of response to treatment in rheumatoid arthritis, only evidence of arrest of the disease or great improvement is significant. Owing to the possibility of spontaneous partial or complete remission in this condition, the great improvement exhibited by 1 of 12 patients is of doubtful importance. One case of slight symptomatic improvement carries even less weight.

Among the 8 active cases there was no demonstrable influence upon the rheumatoid process.

No significant alterations in the blood chemical findings were noted. No toxic reactions occurred.

Recalcification of the bones is a rare phenomenon in active or inactive rheumatoid arthritis<sup>4</sup> within the short periods involved here. It does occur, however, on occasions spontaneously.<sup>5</sup> If it were produced in enough of these patients in such a relatively brief interval, it would indicate therapeutic action confirming some of Helfet's theories for this disease. In all but 1 case the decalcification of the bones was unchanged or had progressed farther. After about fifteen months of aluminum therapy x-ray films in 1 case showed at best a slightly suggestive appearance of recalcification of the bones.

### SUMMARY

Twelve patients with rheumatoid arthritis were treated with aluminum salts for a period of from one to two years.

No appreciable improvement in the subjective and objective signs of activity occurred, nor was the course of the disease significantly influenced in 11 of the 12 patients.

Recalcification of the osteoporotic bones did not appear in the roentgenograms of 8 patients with active rheumatoid arthritis and of 3 inactive cases. In 1 case of inactive rheumatoid arthritis there were suggestive signs of slight recalcification.

Repeated estimations of the blood calcium and phosphorus before and during treatment revealed no significant alterations.

Aluminum subacetate demonstrated no significant therapeutic value in these patients.

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## MEDICAL PROGRESS

## THE ROLE OF PLEUROPNEUMONIA-LIKE ORGANISMS IN GENITOURINARY AND JOINT DISEASES\*

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ORGANISMS belonging to the pleuropneumonia group (L organisms<sup>||</sup>) were first cultured from the human genitourinary tract in 1937<sup>2</sup> and have been recovered from this tract by several investigators since that time.<sup>3-5</sup> No disease in human beings has yet been ascribed to such organisms, although they are known to cause important epizootic diseases in animals. This paper presents further observations on the incidence of these micro-organisms in human beings, with a discussion of their pathogenicity.

The first organism of this type was cultivated in 1898 from cattle<sup>1</sup> and recognized as the cause of one of the most important plagues of this species, bovine pleuropneumonia. It attracted considerable attention because its cultural and microscopical characteristics differed from those of the established classes of micro-organisms. It had properties common to the viruses, being filtrable and invisible in highly infectious tissues or body fluids. In contrast to viruses, however, it could be cultivated in lifeless mediums. Its growth rendered liquid mediums slightly turbid, and on solid mediums numerous tiny colonies developed. The individual organisms could not be seen in the cultures themselves or in the stained smears usually employed in bacteriology. It has since become apparent that the organism is so soft and fragile that it is destroyed during the preparation of the smears. The introduction of appropriate technic, however, has revealed that the cultures consist of small granules and of fine filaments, both of which may swell, forming soft, spherical forms of various sizes. The latter reproduce again the granules and filaments. This reproductive process, which is very different from binary fission, is probably the most characteristic property of the organism. Although the organism differs

considerably from bacteria, the differences between the two groups are only apparent, and the organism of bovine pleuropneumonia is in our opinion, for the reasons given in a previous review,<sup>11</sup> essentially a bacterium.

For twenty-four years this organism was the only one of its kind that was known. In 1923 an organism of similar properties was discovered as the cause of the disease known as agalactia in goats and sheep.<sup>12</sup> During the past twelve years similar organisms have been recovered from dogs, rats, mice and human beings, and have been found as saprophytic organisms in sewage and soil.<sup>13</sup> The most surprising finding has been the discovery of organisms with similar properties in cultures of various bacteria.<sup>11,14</sup> The majority of investigators now consider these to be variant growth forms of the bacteria.<sup>11</sup>

Whatever their source all pleuropneumonia strains are closely similar in the appearance of their colonies, in morphology, in staining and in physical properties. The bovine, goat and rat strains are pathogenic and produce well known diseases. The mouse strains, usually harmless saprophytes, are pathogenic if introduced artificially into mice. All pathogenic strains produce diseases that tend to be chronic. Although the primary localization of the process varies, joint involvement is common in all species of animals. Usually there is a migratory polyarthritis that subsides entirely within a few weeks, but occasionally the joint involvement is more severe, with suppuration and subsequent destruction of articulating surfaces and ankylosis. In mice, intravenous injection of one type of pleuropneumonia organisms (Type B) has been found to produce a chronic, proliferative process leading in many cases to ankylosis of the involved joints in two to five months.<sup>15</sup>

The pleuropneumonia-like organisms can be recognized only by culture. Identification cannot be made in microscopical preparations from lesions since the organisms are usually not visible in stained preparations and are not sufficiently characteristic in dark-field examination. Since the human strains are not pathogenic for laboratory animals, they cannot be recognized by animal inoculations. Cultures, however, are characteristic. Many human strains grow well on mediums used for cultivation of

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||Klebschneider used the letter "L" to designate the strains of the pleuropneumonia group that he isolated.



gonococci, provided the mediums contain animal or human serum. We have obtained the best results with sedimented boiled blood agar to which 30 per cent ascitic fluid or 20 per cent human serum has

be recognized only in microscopical preparations. Stained agar preparations are the most appropriate for this purpose. A square of agar from a suspicious area on the plate is placed on a slide. It is covered with a coverslip on which an alcoholic solution of methylene blue and azure has been dried. The space surrounding the agar square between the coverslip and slide is filled with molten paraffin. It is necessary in making these preparations to avoid large bacterial colonies because they often decolorize the stain. The appearance of L colonies

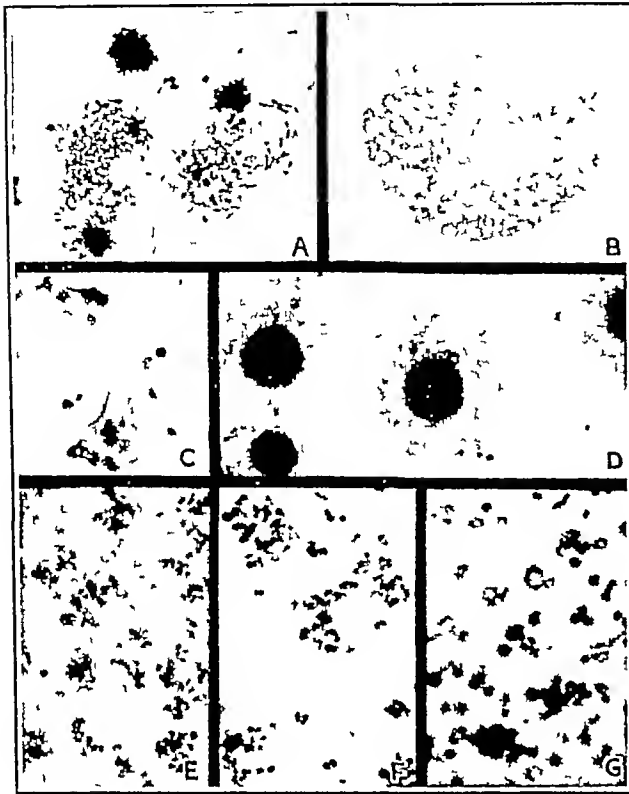


FIGURE 1

A shows a wet, stained-agar preparation of a two-day-old culture from the uterine cervix in which the colonies of the pleuropneumonia-like organisms are deeply stained — the flat, slightly stained colonies are diphtheroids ( $\times 600$ ). B shows a wet, stained-agar preparation of a fully developed colony of pleuropneumonia-like organisms, demonstrating the transformation of the organisms into large round bodies, taken from a pure culture ( $\times 600$ ). C shows sixteen-hour colonies grown from the urinary sediment of a male patient, the tiny colonies being in clusters on and beneath the epithelial cells and a few separate colonies appearing on the agar surface, this photomicrograph was made from a dry-impression preparation, thus making the epithelial cells visible ( $\times 125$ ). D shows the same culture after seventy-two hours' incubation, the periphery of the colonies consisting of small bacillary forms like those illustrated in F and G below ( $\times 125$ ). E shows a wet, stained-agar preparation of young colonies of pleuropneumonia-like organisms in pure culture — the individual organisms are not clearly visible because all colonies were not in the same plane ( $\times 1250$ ). F shows an impression preparation of young colonies on agar after fixation of the agar with Bouin's solution in which the organisms appear as small polar-stained bacilli, Giemsa stain was used ( $\times 2000$ ). G shows a Giemsa-stained preparation from a broth culture in which small polar-stained bacillary forms, ring forms and markedly swollen forms are visible ( $\times 2000$ ).

been added.<sup>15</sup> Anaerobic conditions are necessary for many strains. The colonies are well developed in two or three days. Sometimes they are macroscopically visible as pin-point colonies, but often they are only 10 to 20 microns in diameter and can

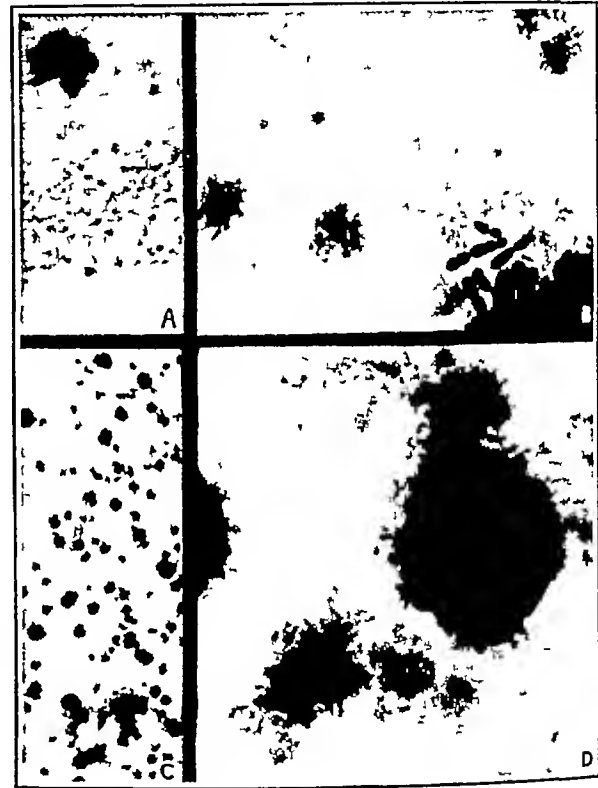


FIGURE 2 Colonies of Pleuropneumonia-like Organisms in Cultures Made Directly from Specimens, as They Appear in Wet, Stained-Agar Preparations with Low (A and C) and with High (B and D) Magnification

A shows tiny colonies and a small streptococcus colony from a male urethra ( $\times 200$ ). B shows part of the former under high magnification, demonstrating the edge of the streptococcus colony and a few pleuropneumonia-like colonies after two days of incubation — the colonies in this case did not develop to a larger size ( $\times 2000$ ). C shows medium-sized colonies from a prostatic secretion after one day of incubation ( $\times 200$ ). D shows small and medium-sized pleuropneumonia-like colonies from a urinary sediment after sixteen hours' incubation — the contours of two epithelial cells are noticeable in the photograph ( $\times 2000$ ).

in such preparations is so characteristic that they cannot be mistaken for anything else by an experienced observer (Fig 1 and 2). Under suitable conditions, even the tiniest colonies can be recognized. Whether small or large, the colonies not only extend on the surface but also invade the medium. The young colonies consist of small granules, which stain less deeply and are less refractile than bacteria

The organisms on the surface of large colonies grow to large round bodies (10 microns or more in diameter), and as a result of the autolysis of many of these bodies, a foam-like structure develops at the edge of the colonies (Fig 1 B). Because of the softness of the organisms, some of them are always distorted and pulled out to filaments in preparations. The softness of the organism, the formation of large bodies and the extension of the colonies into the medium distinguish the pleuropneumonia-like organisms from other bacteria.

The methods of anaerobic culture and stained agar preparations used in the present study have made possible the detection of pleuropneumonia-like organisms in many cases of genitourinary-tract infection in males in which the organisms would otherwise not have been recognized. These methods have been important also in differentiating pleuropneumonia-like organisms from pleomorphic forms of other bacteria. The procedures differ in many respects from those used by other workers. Microscopical examination of unstained colonies and dark-field examination of broth cultures are unsatisfactory and often misleading. The impression preparations used by Klieneberger<sup>1</sup> and Salaman<sup>2</sup> may lead to errors in the recognition and identification of pleuropneumonia-like organisms since the small colonies cannot be seen and the large colonies are identified merely by the surface layer, the only part that adheres to the glass. This surface layer cannot be distinguished in such preparations from that of colonies of pleomorphic bacteria in which individual organisms swell into large spherical forms.

The tendency toward the production of pleomorphic forms of common bacteria, which are difficult to differentiate from pleuropneumonia-like organisms, is greatly increased by addition of penicillin to the medium to suppress bacterial growth. In our laboratory large spherical bodies have been produced from gram-negative bacilli and from gonococci and other Neisseriae on penicillin-containing medium. With certain bacteria, such as *Haemophilus influenzae* and *Escherichia coli*, the presence of penicillin causes the appearance of organisms that have all the characteristics of the pleuropneumonia group. In this paper, cases from which pleuropneumonia-like organisms were cultured only when antibiotics were given to the patient or were added to the culture medium are not included in the series and are considered only in the discussion.

The pleuropneumonia-like organisms that are cultivated from human beings and that have no apparent relation to other bacteria are characterized at present only by their morphologic and physical properties. It is probable that they do not belong to a single species but represent many strains, which, like the mouse strains, are different in pathogenic action and serologic properties. However, the properties useful in differentiating strains of morphologically similar bacteria, such as growth require-

ments, metabolism and pathogenicity, are not known in these organisms. The cultural differences that we have observed which may or may not represent differences between species, are variation in appearance and size of colonies and difference in adaptation to artificial mediums. Organisms obtained from the female genital tract can usually be cultivated without difficulty. The colonies reach a relatively large size (0.1 to 0.5 mm) and grow easily in transplants. Culture from males is more difficult. In several male patients with severe inflammation of the genitourinary tract, the organism grew only anaerobically. The colonies remained very small (0.01 to 0.05 mm) and in transplants the organisms either did not grow or died out in two or three subcultures. Nelson<sup>11</sup> experienced difficulty in cultivating an organism with similar properties that he isolated from a coryza of chickens. It grew at first in tissue culture alone and started to grow in lifeless mediums only after one hundred and twenty passages. The culture method that we have used is presumably not appropriate for all strains, and with this technic we probably do not succeed in growing the organism from all specimens in which it is present.

Little is known about the serologic properties and pathogenic activity of the human strains, although some serologic differences between strains have been demonstrated.<sup>17</sup> Warren and Sabin<sup>18</sup> studied a human strain isolated by us. They concurred in its classification in the pleuropneumonia group and found it to be serologically different from strains isolated from animals. The human strains have not been pathogenic for mice, rats or guinea pigs except in one litter of young mice that died two to six days after infection.<sup>2</sup> Using antigen prepared from two strains of pleuropneumonia-like organisms isolated from patients with nonspecific urethritis, Beveridge, Campbell and Lind<sup>9</sup> obtained positive complement-fixation tests in 33 and 92 per cent of serums in two series of cases of nonspecific urethritis. However, positive results were obtained also in 7 and 70 per cent of two control series. The serologic studies reported by Wallerstein, Vallee and Turner<sup>19</sup> are difficult to interpret, since the organism used, though resembling the pleuropneumonia-like organisms in a few respects, could not be differentiated from the *Grahamella*. Abundant growth that can be washed from agar mediums such as that reported has not been observed by any investigators with organisms of the pleuropneumonia group.

In human beings the pleuropneumonia-like organisms were discovered first in the female and later in the male genitourinary tract. Material from various other sources, including secretions from the respiratory tract and conjunctiva, pleural, synovial, and spinal fluids and stools, has been examined with similar methods, but, in the absence of penicillin, all cultures have been negative for these organisms with the exception of synovial fluids from 2 pa-

Reiter's syndrome discussed below \* The material cultured included 30 throat swabbings from patients with upper respiratory infections and 15 from cases of active rheumatic fever with or without pharyngitis, 24 tonsils excised for chronic tonsillitis, secretions from 4 healthy conjunctivas and 9 cases of conjunctivitis, joint fluids from 15 cases of rheumatoid arthritis, and 15 stool specimens Beveridge, Campbell and Lind<sup>9</sup> found no pleuropneumonia-like organisms in 4 patients with atypical pneumonia, in 57 washings from infected antra or in 70 excised tonsils Perhaps the discovery of more appropriate

TABLE 1 *Clinical Findings in the 58 Women Yielding L Organisms in Cultures from the Cervix or Vagina*

CONDITION OF PATIENT	NO OF CASES
No history or evidence of genitourinary disease	8
Trichomonas vaginitis	9
Gonorrhea (both gonococci and L organisms present in cultures)	11
Recent gonorrhea	9
No discharge	6
Discharge persisting but gonococci no longer demonstrable	3
Leukorrhea	21
Variety of organisms present in addition to L organisms	16
L organisms found in pure or nearly pure culture	5

media and more extensive use of anaerobic cultivation will demonstrate the presence of the L organism in some of these locations

Cultivation of pleuropneumonia-like organisms in human beings from sites other than the genitourinary tract has been reported only by Herschberger, Dantes and Schwartzman<sup>20</sup> In blood cultures from a patient with subacute bacterial endocarditis they found an organism that they were unable to identify From their description it seems probable, as mentioned above, that the organism did not belong to the pleuropneumonia group but, as the authors suggest, to the *Grahamella*

After the discovery of L organisms in an abscess of a Bartholin's gland in 1937,<sup>2</sup> a study was undertaken to determine the incidence of these organisms in the human genitourinary tract † All routine genitourinary specimens sent to the bacteriologic laboratory over a period of three months were examined for L organisms The specimens were, in most cases, submitted for examination for gonococci and were planted immediately by the physician taking the specimen on 30 per cent ascitic-fluid-infusion agar plates containing 1 per cent neopeptone

\*Pleuropneumonia-like organisms have been found in cultures from the respiratory tract when penicillin has been given to the patient or added to the cultures to suppress bacterial growth As pointed out above, these organisms represent a variant growth form of other bacteria, often *H. influenzae* In a series of 17 throat and sputum cultures in which penicillin was added to the medium pleuropneumonia-like organisms were isolated in 12 whereas the same specimens cultured on penicillin-free media were negative for L organisms Similar organisms, together with *H. influenzae*, were cultured from the sputum of a patient with lung abscess intensively treated with penicillin aerosol and from a suppurative lesion of the jaw treated with penicillin In all these cases the pleuropneumonia-like organisms were variants of other bacteria produced under the influence of penicillin Nothing is known of their pathogenicity

†We are indebted to Drs J V Meigs and Langdon Parsons of the Massachusetts General Hospital for their aid in carrying out this study

and 2 per cent boiled horse blood This series included 214 specimens from the uterine cervix and 8 from the vagina, urethral discharges from 4 female patients, purulent material from 18 patients with suppurative processes connected with the female genital tract (Table 2), 60 prostatic secretions and purulent discharges from 11 male patients with urethritis The L organism was present in 26 per cent of the cervical cultures of the above series (Table 2) It was also found in the suppurative processes originating from the female genital tract but in a lower proportion of cases

The incidence in the female genitourinary tract in this series was in the same range as that reported by other investigators Klieneberger-Nobel<sup>15</sup> found L organisms in only 14 per cent of 50 pregnant women but noted a much higher incidence (33 to 40 per cent) in the vagina in women with pathologic conditions of the genitourinary tract Similarly, Salaman<sup>8</sup> reported much higher percentages of positive cultures (44 to 75 per cent) in women with various inflammatory conditions of the genitourinary tract than in normal women (6 per cent) Beveridge, Campbell and Lind<sup>9</sup> obtained positive cultures in 17 per cent of 101 "apparently normal women" attending the gynecologic clinic

Clinical data on the 58 women of the original series with positive L cultures are presented in Table 1 The organism was present in 6 cases without any evidence or history of genitourinary disease It was associated with the gonococcus in 11 cases and remained in the cervix after the gonococci disappeared The relatively high incidence of

TABLE 2 *Recovery of Pleuropneumonia-Like (L) Organisms from an Unselected Series of Specimens from the Human Genitourinary Tract*

SOURCE	TOTAL NO OF PATIENTS	PATIENTS WITH L ORGANISMS	PER CENTAGE
Cervical secretion	214	56	26
Vaginal secretion	8	2	25
Urethral discharge (female patients)	4	0	0
Bartholin abscess	6	1	17
Salpingitis	8	1	13
Peritonitis arising from salpingitis	4	1	25
Prostatic secretion	60	5	8
Urethral discharge (male patients)	11	1	9

this organism in the female genital tract suggests that it is part of the bacterial flora in this location However, its presence in suppurative processes suggests that it occasionally has some pathogenic action in the female genital tract Since the original series of unselected cases was completed, we have searched for L organisms in various types of inflammation of the female genitourinary tract and have obtained further suggestion of its pathogenicity We have cultivated the organism from Bartholin's abscesses in 6 cases and from a pelvic abscess associated with puerperal infection and from one associated with salpingitis The organism was associated

with other bacteria except in 2 cases of Bartholin's abscess (Case 1)\*. In 6 cases of acute and chronic vaginitis and cervicitis the *L* organism was present in pure culture (as in Case 2) and in 17 other cases was found in much greater abundance than other bacteria. In some of these cases the acute inflammatory condition developed a few days after sexual exposure. Such observations lend support to the hypothesis that the organism is pathogenic under certain conditions and indicate the necessity for further studies of its role in inflammatory conditions of the female genitourinary tract.

In male patients the incidence of *L* organisms in the genitourinary tract is much lower than that in females. In the original series of routine cultures discussed above, the incidence in males was 8 per cent (Table 2). Beveridge<sup>6</sup> isolated pleuropneumonia-like organisms in 4 of 24 cases of nongonococcal urethritis in males. Salaman<sup>8</sup> found *L* organisms in 4 out of 28 men without any evidence of urethritis and in 3 of 45 cases of nonspecific urethritis. Johnston<sup>7</sup> isolated *L* organisms in 2 cases of nonspecific urethritis. Beveridge, Campbell and Lind<sup>9</sup> cultured pleuropneumonia-like organisms from 14 of 70 urethral washings from patients with nonspecific urethritis, from 67 normal male medical students they obtained no positive cultures. The incidence in these series might have been higher if stained agar preparations had been used since small *L* colonies may not have been recognized by the methods employed.

This difference in incidence of *L* organisms in the male and female genitourinary tracts has also been apparent in the many cultures taken during and after gonococcal infections, examined since the original series of unselected specimens was completed. These specimens have also afforded opportunity to determine the frequency of association of gonococci and *L* organisms in the genitourinary tract. In cultures from female patients the two organisms were often found together. In our original series the *L* organism was found in association with the gonococcus in 11 female patients, and in the 5 cases followed, the *L* organisms remained in the cervix after the gonococci had disappeared. In male patients, on the other hand, none of the 6 cultures that showed gonococci were positive for the *L* organism. In fact, *L* organisms have been found, in our laboratory, in only 2 cultures from the male urethra or prostate that were positive for gonococci and in only 1 case in cultures obtained immediately after the cure of a gonococcal infection. It is apparent that pleuropneumonia-like organisms are not common inhabitants of the male genitourinary tract as they are in female patients. Salaman<sup>8</sup> reported positive cultures for *L* organisms in 12 of 35 cases of gonorrhea in men. However, as mentioned above, the addition of penicillin to the

culture medium causes production of large spherical forms of gonococci and other bacteria, and differentiation of such pleomorphic forms from pleuropneumonia-like organisms is extremely difficult in the impression preparations used by him.

A study of the male patients from whom positive cultures for pleuropneumonia-like organisms were obtained gave more definite evidence of the pathogenicity of these organisms than that in the female patients. The organisms have been found in 58 male patients, including the 6 cases in the original routine series (Table 2). All had evidence of prostatitis or other genitourinary-tract infection at the time of the isolation of the organism. In 1 patient (Case 12) *L* organisms were first cultured from the prostate during an acute attack of urethritis, arthritis and intis. Eighteen months later cultures of the prostatic secretion were negative for *L* organisms. However, during an attack of urethritis, arthritis and conjunctivitis, apparently precipitated by prostatic massage, an abundant growth of *L* organisms in pure culture was obtained from the prostate. In 12 cases the *L* organisms were grown in pure culture. Six of these patients had cystitis (as in Case 11). Another had a penurethral abscess. In the 4 cases of cystitis followed *L* organisms disappeared or decreased markedly in number after the urinary symptoms subsided. These data offer strong evidence that the pleuropneumonia-like organisms were the cause of the urinary-tract infection.

In a control series of 31 patients with chronic, nongonococcal prostatitis, only 1 of the prostatic cultures contained *L* organisms. The technique of culture and examination was the same as that used in the cases of acute or subacute prostatitis in which prostatic cultures were positive for *L* organisms.

Clinical data on the male patients can be presented best if the cases are divided into groups. These presumably indicate the various clinical pictures produced by infection with pleuropneumonia-like organisms. The groups are discussed separately so far as possible, and cases characteristic of each type are presented. Ninety per cent of the patients were between the ages of twenty and forty. In all groups the severity of involvement varied greatly.

In 26 cases the infection was limited to the urethra and prostate without cystitis, arthritis or conjunctivitis. The evidence of urethritis varied, approximately a third of the cases had only a slight discharge (or slight burning on urination) lasting a few days or months (as in Case 3), whereas the remainder had a moderate or profuse purulent discharge persisting for months or even years (as in Case 4). One patient had a penurethral abscess of two days' duration. Similarly, the prostatitis was manifested in a third of the cases merely by slight change in the size and texture of the prostate and a few white cells in the secretion, but in others the gland became large, boggy and tender and massage produced purulent secretion. In 5 cases pure cultures of

\* In 1 case anaerobic cultures were not made so that the possibility that other anaerobic bacteria were present could not be ruled out.

L organisms were obtained from the urethral secretions. In most of this group there was no evidence of systemic involvement, but 2 patients had an erythematous maculopapular rash.

In 9 cases the infection involved the bladder. Symptoms in these patients varied from slight dysuria and frequency in 2 cases to severe pain or gross hematuria in the remaining 7. Severe hemorrhagic cystitis was demonstrated by cystoscopy in 4 cases. The urine yielded abundant growth of pleuropneumonia-like organisms in pure culture in 6 cases and was associated with a few colonies of diphtheroids, staphylococci, *Esch coli* or streptococci in the others. In a higher percentage of these patients with cystitis (8 of 9 cases) than in those with

or iritis who presented the typical picture of Reiter's syndrome.

In the patients with chronic joint involvement, the evidence of urinary-tract infection antedated the onset of the arthritis in all but 1 patient, a sixty-nine-year-old man with typical rheumatoid arthritis of thirty-three years' duration. The joint symptoms in this group consisted usually of stiffness, aching and slight swelling that persisted for months or years (as in Case 6). It is impossible to determine whether there was any relation between the joint involvement and the urinary-tract infection in these cases.

The joint involvement in the acute cases was usually sudden in onset, polyarticular and often

TABLE 3 Synovial-Fluid Findings in Male Patients with Positive Cultures for Pleuropneumonia-Like Organisms\*

CASE No †	JOINT	CLOT	WHITE CELLS per cubic millimeter	POLYMORPHO- NUCLEAR CELLS %	SUGAR		RELATIVE VISCOSITY at 38°C	MUCIN TYPE OF PRECIPITATE
					SERUM mg /100 cc	FLUID mg /100 cc		
327889	Right knee	—	650	72	95	90	—	Excellent
	Right ankle	—	6 100	88	—	—	—	—
516121	Right knee	++++	8 200	65	95	90	5 6	Poor
J E	Left knee	+++	2 050	67	90	84	9 4	Poor
352561	Left knee	+++	2 500	64	80	83	13 8	Good
315068	Left knee	+++	56 400	88	—	—	23	Fair
348216	Right knee	—	5 050	9	—	90	5 5	Good
R F	Left knee	++++	32 550	87	106	65	3 1	Very poor
440884	Left knee	+++	9 200	51	98	94	11 9	Excellent
255127								
1/29/46	Right knee	++	20,700	77	112	109	7 4	Good
1/29/46	Left knee	+	12,400	56	112	111	16 3	Good
9/20/46	Right knee	++	52 800	79	—	—	9 3	Fair
J D	Right knee	+++	11,200	37	—	71	10 6	Fair
	Left knee	+++	—	—	—	66	16 9	Fair
273497	Right knee	+++	23 750	62	—	—	15 5	Fair
	Left knee	—	15,200	53	90	84	4 2	Poor
E R	Right knee	—	3,300	54	—	—	—	Good
W M	Right knee	++	—	—	—	—	—	Fair

\*In all patients pleuropneumonia like organisms were cultured from the genitourinary tract and in patient R F and Case 440884 from the synovial fluid.

†The cases without numbers were from outside hospitals. The last 7 cases presented the characteristic picture of Reiter's syndrome.

uncomplicated urethritis and prostatitis, the infection persisted for many weeks. In 3 cases it recurred frequently over the course of several years. It is in this group that the effect of streptomycin therapy was most impressive, as pointed out below. Evidence of systemic involvement was present in only 2 of these patients. They had the characteristic picture of Reiter's syndrome and are discussed in that group.

The presence of constitutional symptoms (fever, chills and malaise) and joint involvement in many of the male patients with positive cultures for pleuropneumonia-like organisms suggests that these organisms produce a generalized infection with joint localization. Arthritis was present in 27 cases, but the type varied considerably. They can be divided into cases with subacute or chronic joint involvement (9 cases) and those resembling infectious arthritis in the acuteness of onset, the tendency to migration and the degree of pain, tenderness and heat of the involved joints (18 cases). The acute group can be further subdivided into 9 cases without eye involvement and 9 patients with conjunctivitis

migratory (Cases 7, 8 and 9). In 6 cases it was associated with fever and malaise and in 2 cases with chills. Two patients had skin rashes, maculopapular in 1 and vesicular in the other, and another had a balanitis. The affected joints were usually swollen, very painful and tender and occasionally somewhat reddened. The effusions usually persisted for long periods, often for months. The cytologic and chemical findings in the synovial fluids obtained in 6 cases are summarized in Table 3. The total leukocyte and polymorphonuclear counts were lower and the sugar contents higher than those found in comparable cases of infectious arthritis due to pyogenic organisms.<sup>21</sup> Similarly, the mucin precipitated with acetic acid formed a tighter clump in most of these fluids than in effusions from other types of infectious arthritis. Despite the evidence of rather severe inflammation given by the synovial-fluid findings (Table 3), the only roentgenographic change observed to date is moderate decalcification of the bones around the involved joints.

The clinical picture in 9 cases was characteristic of Reiter's syndrome, consisting of urethritis, arthri-

tis and conjunctivitis (Cases 11 and 12). The genito-urinary and joint involvement resembled that of the other cases with acute arthritis. The synovial-fluid findings in 7 cases are given in Table 3. The conjunctivitis was usually moderately severe, often with purulent discharge and persisting for one or two weeks. In 2 cases there was only slight redness, burning and discharge lasting one or two days. Iritis was present in 2 of the cases, but no patients had corneal ulcers. Balanitis, consisting of superficial papulovesicular or ulcerated lesions, was noted in 5 patients. Stomatitis was present in 2 of these. Three patients had generalized skin lesions, maculopapular and vesicular. Aspiration of vesicles on the plantar surface of the foot in 2 of these cases yielded amorphous material, cultures of which were sterile. Like the patients with uncomplicated urethritis and prostatitis due to the pleuropneumonia-like organisms, the patients with Reiter's syndrome showed a tendency toward recurrence of the disease, 5 out of 9 having recurrences. One patient (Case 12) has been seen in 5 attacks during the past six years.

(To be concluded)

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## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Stated Meeting, February 4, 1948

A STATED meeting of the Council was called to order by the president, Dr Edward P Bagg, Hampden, on Wednesday, February 4, 1948, at 10 30 a m in John Ware Hall, 8 Fenway, Boston One hundred and ninety-seven councilors (Appendix No 1) were present

After opening the meeting and introducing the new secretary, Dr H Quimby Gallupe, Middlesex South, the President read the following obituary

WILLIAM J PELLETIER — "No physician, insofar as he is a physician, considers his own good in what he prescribes, but the good of the patient" according to the pronouncement of Plato in the third century B C The truth of this axiom, particularly regarding the physician's own health, has been demonstrated once more to our profound sorrow in the twentieth century, A D, through the death in the prime of life of our fellow councilor, William J Pelletier, who had just turned fifty years

One of Tufts' most brilliant graduates, he furnished an outstanding example of what a talented physician can mean in the life of a smaller community, not only by the skillful laying on of hands but also by the breadth of his interests and the strength of his upright, friendly character Throughout the upper Pioneer Valley, he was favorably known as a practitioner of medicine As a surgeon, he won membership in the American College of Surgeons For years he handled acceptably the medicolegal problems of the Eastern District of Franklin County as associate and since 1943 as chief medical examiner

Dr Pelletier volunteered for military service in the United States Army in World War I During World War II he acted as physician to his Selective Service board when disabilities kept him out of uniform

A past president of the Franklin District Medical Society and long-time member of the Council, he was always alert and ready, so long as his strength permitted, for whatever work was assigned to him in the Massachusetts Medical Society His counsel will be missed in the affairs that concern us all, but even more so in his hometown, Turners Falls, where he served so splendidly as a citizen in various capacities, including those of school physician and member of the Board of Health Most acutely, outside the family circle, the Farren Memorial Hospital will suffer through the loss of Dr Pelletier, a former president, who did so much to improve the facilities of the institution in anticipation of the growing clinical needs of his fellow citizens

Like Dorcas of Joppa, this man was "full of good works and alms-deeds which he did" A modern Luke, he was a beloved physician worthy of the name who did not "live unto himself" alone

May peace be his reward, well deserved and without end

The President then said that he had just been notified of the passing of Dr Isaac S F Dodd, of Pittsfield, vice-president of the society in 1947, and that since it was impossible on such short notice to do justice to his work and character, he was postponing his memorial until the next Council meeting

At the request of the President, the Council stood for one minute in silent tribute to the two departed members of the Council

The Secretary presented the record of the October, 1947, meeting of the Council as published in the

*New England Journal of Medicine*, issue of December 4, 1947, and moved its acceptance The motion was seconded by Dr Eliot Hubbard, Middlesex South, and it was so ordered by vote of the Council

## APPOINTMENTS

The President then announced the following interim appointments

To the Committee on Postgraduate Medical Education Dr John F Conlin, Suffolk, to replace Dr Robert N Nye, deceased

To Represent the Massachusetts Medical Society on the Board of Trustees of the Boston Medical Library, retroactive to January 1, 1948

Dr Curtis C Tripp, New Bedford, to serve for 1948

Dr John J Curley, Leominster, to serve for 1948-1949

Dr Edward S O'Keefe, Lynn, to serve for 1948-1949-1950

Dr Albert Ehrenfried, Boston, to serve for 1948-1949-1950-1951

Delegates to Annual Meetings of New England State Medical Societies

Connecticut, Dr Raymond L Barrett, Springfield  
Alternate, Dr John Pallo, Westfield

New Hampshire, Dr William M Collins, Lowell  
Alternate, Dr Ralph E Cole, Westford

Maine, Dr Harold G Giddings, Boston  
Alternate, Dr Lincoln C Peirce, Newburyport

Rhode Island, Dr Harold E Perry, New Bedford  
Alternate, Dr William Mason, Fall River

Vermont, Dr Warren D Thomas, Montague  
Alternate, Dr John B Temple, Shelburne Falls

The President asked for confirmation of these appointments, and it was so ordered by vote of the Council

## REPORTS OF COMMITTEES

Committee on Public Relations — Dr Harold R Kurth, Essex North, Secretary

President Bagg stated that according to the circular of advance information (Appendix No 2) the first item was to consider whether or not to approve the objectives of the National Physicians Committee, and that Dr Channing Frothingham had been given a hearing before the Committee on Public Relations, since time was not sufficient at the last meeting of the Council Also, a letter from Dr Frothingham had been published in the *New England Journal of Medicine*, issue of November 20, 1947

The National Physicians Committee had sent Mr M H Peterson to attend the last meeting of the Executive Committee The President asked the Secretary to read a résumé of Mr Peterson's remarks (Appendix No 3)

The Secretary then moved the approval of the objectives of the National Physicians Committee. This motion was seconded.

Dr Channing Frothingham opened the discussion as follows:

I should like to say that as I go around the country not only among the laymen but also among the medical profession there are a good many people who doubt the sincerity of the National Physicians Committee and also admitting that the National Physicians Committee is sincere, there are a good many who do not approve of its methods.

Later this morning you will be asked to raise your contribution for information regarding medical legislative service which is produced by Marjorie Shearon and I should like to give a short quotation from Marjorie Shearon concerning the National Physicians Committee:

The National Physicians Committee is still another inimical force working against the medical profession from within. This organization I regard as second only to the medical politicians in their threat to American medicine.

A letter from Marjorie Shearon which she sent around to members of the medical profession and others interested contains the following statements:

I have refused to co-operate with the National Physicians Committee because the publications of that committee have been misleading and have failed to give to the medical profession the carefully prepared scientifically accurate and objectively informative material which the profession should have.

The facts about nationalization of medicine speak for themselves and are embellished are sufficiently alarming.

Evidence given at the hearing on S 1606 indicates the National Physicians Committee receives a considerable proportion of its backing from the drug industry. Why should the medical profession which is a reputable and honorable one altruistically devoted to the service of humanity have its educational campaign or more correctly speaking its legislative lobbying activities financed in considerable measure by a purely commercial group such as the drug industry?

The National Physicians Committee from its own testimony appears to be vulnerable in its dealings with the Bureau of Internal Revenue.

Mr Edward F Stegen associate administrator of the National Physicians Committee has not in my opinion, conducted himself in accordance with accepted professional standards of conduct.

The Washington representative of the National Physicians Committee, Arthur L. Conrad, associate administrator of the National Physicians Committee, in my opinion is exceptionally unqualified to represent the physicians and surgeons of the United States.

I am not convinced the National Physicians Committee discussion groups which early in May delivered a statement of high policy regarding national health legislation really represented the medical profession or was working in the best interests of the profession.

I doubt if the members of the Board of Trustees of the National Physicians Committee who are I take it physicians of high standing and unquestioned probity have any clear picture of what goes on in Washington in their name.

For these reasons I urge the Council to explore the sincerity and activity of the National Physicians Committee before giving it its stamp of approval.

President Bagg asked for any further discussion. Dr Reginald Fitz, Suffolk, drew attention to the fact that the committee to meet with the Committee on Medical Economics had not reported and that Dr Gallupe's motion was out of order, and Dr Fitz moved that the motion to approve be tabled.

until the report of the committee was received. Dr Carl Bearse, Norfolk, seconded this motion. It was so voted.

Dr Bagg stated that the matter could be referred back to the Committee on Medical Economics.

Dr Bagg then stated that the matters concerning Blue Shield, referred to Dr McCann's subcommittee, would be resubmitted to the Committee on Public Relations at the next meeting.

Dr Bagg then called attention to a resolution in the report of the Executive Committee report (Appendix No 4) in which Dr Curley moved to approve the changes in the by-laws suggested in a letter from Dr Bagoall, to the effect that the president of Massachusetts Medical Service, Inc, and the medical director thereof be made members of the Council. This motion was seconded by Dr Wheeler and unanimously approved by the Executive Committee.

Dr Bagg asked the pleasure of the Council. Dr Curley then repeated his motion, which Dr Wheeler seconded. Dr Bagnall offered the following amendment to the motion: "If the president of Massachusetts Medical Service be a physician, and a member of the Massachusetts Medical Society" because the president might not be a physician, and therefore would not be eligible for membership in the Council. Dr Curley accepted the amendment. Dr Bagg called for a vote. The motion was carried.

Dr Bagg then called attention to a statement of Dr Appel's as follows: "The medical staff of the Salem Hospital unanimously opposed the inclusion of professional services in the Blue Cross policy."

Dr Bagg then spoke as follows:

This item was referred to Dr McCann's committee. It seems to me pertinent to speak at this time of the present status of the report of the Special Services Committee which had to do with that topic, and I should like to read you a letter that I wrote to Dr Parkhurst, chairman of the Committee to Meet with the Massachusetts Hospital Association. This is under date of January 30.

Two hundred copies of the reprints of the report of the Committee on Special Services have been sent to the president of the Massachusetts Hospital Association for distribution to member hospitals. After consulting with members of the Committee on Public Relations it seems proper to refer these stated principles of the physician hospital relations to your committee to meet with the Massachusetts Hospital Association.

I should like to add the name of Leland S. McKuttrick to your Committee inasmuch as he was chairman of the Special Services Committee, and is vitally interested in the matter.

The ultimate application of these principles of course must rest with the members of the Society who compose the medical staffs of individual hospitals. Approval of the Council for this action will be sought at the next stated meeting.

That is today. I have a letter under date of January 28 from the secretary of the Massachusetts Hospital Association, as follows:

We are today in receipt of 200 reprints of the Report of the Committee on Special Services. They are being mailed out today to member hospitals.

As you recall that report was approved at the October meeting of the Council and it was published in the *Journal* in December. The difficulty that has held it up so long



was to get reprints. They were finally made available, after the middle of January, and they have gone out.

I have a letter from Dr McKittrick stating that he would be very glad to serve, if the Council so wishes. What I should like to know now is whether the Council approves of this disposition of the matter.

Dr Hornor moved approval of the President's action. The motion was seconded by Dr Bagnall and unanimously voted by the Council.

Dr Bagg then asked Dr John F Conlin to report on the Women's Auxiliary and other matters.

Dr Conlin then stated that three auxiliaries had been organized and six others were in the process of organization. He asked the co-operation of the officers of the district medical societies toward the formation of auxiliaries so that a state auxiliary could be formed.

Dr Bagg then asked for approval of the recommendations to expend \$50 to help the State Nurses' Association publish a fact sheet on schools of nursing in Massachusetts.

Dr O'Hara moved that the recommendation be approved. Dr Bagnall seconded the motion, which was carried.

Dr Bagg asked the pleasure of the Council regarding the approval given by the Executive Committee to the action of the Public Relations Committee in increasing the fee of the Marjorie Shearon Service from \$200 to \$500.

Dr Dunlop moved to increase the fee for the Service from \$200 to \$500.

The motion was seconded. It was then discussed by Drs Channing Frothingham, Dwight O'Hara, Elmer Bagnall, Augustus Thorndike and Reginald Fitz.

Dr Buck explained that the Committee on Finance had approved the expenditure by the Committee on Public Relations as reasonable. Dr Bagnall stated that the matter was one of approval or not of the President's action in emergency appropriations. Dr Leroy E Parkins, Suffolk, questioned the importance of the Shearon Service.

Dr Allan M Butler, Suffolk, stated that the committee had a right to buy information needed but questioned the advisability of the Society's subscribing to a particular service.

Dr Bagg stated the question. The motion was passed by a majority vote.

Dr Ober moved the approval of the report as a whole. Dr O'Hara seconded this motion, and since there was no discussion, the motion was carried.

#### STANDING COMMITTEES

*Committee on Publications* — Dr Richard M Smith, Suffolk, *Chairman*.

This report, which is as follows, was presented by Dr Smith.

The Committee on Publications wishes to submit an amendment to the by-laws of the Society, in Chapter IV, Section 1, as follows: omitting the word "and" in the last

portion and substituting a comma, and adding after "committees," the phrase, "and the editor of *The New England Journal of Medicine*." The whole Section will then read:

Section 1. The Council shall consist of counselors chosen by the district societies, the president, ex-presidents, president-elect, vice-president, vice-presidents *ex-officio*, secretary, treasurer, and assistant treasurer of the Society, the secretaries of the district societies, the chairmen of all standing committees and the editor of the *New England Journal of Medicine*.

Dr Smith moved acceptance of the report. Dr Parkins seconded the motion.

Dr Bearse, Norfolk, spoke as follows:

Mr President, I feel at the present moment like a man who is a day late to a funeral. In this present report a recommendation has been made that the by-laws be amended — well, the by-laws have been amended so that the editor of the *New England Journal of Medicine* would be a member of the Council, *ex-officio*.

This particular recommendation has been made very correctly, but when it comes to amending the by-laws, according to the by-laws under which we are now operating, there is a definite formula to be followed.

In the report of the Committee on Publications, that formula has been followed.

Earlier this morning the Council voted to accept a motion to the effect that the director of the Blue Shield and the president of the Board of Directors of the Blue Shield and the medical director be made members of the Council, *ex-officio*.

In order to have this done, a similar motion should have been introduced, as has been done by the Committee on Publications. The by-laws state in Chapter 9, amendments, "These by-laws may be amended by a majority vote at any annual meeting of the Society, provided that the proposed amendment or amendments shall have been submitted previously in writing to the Council."

So far as the action taken by the Council pertaining to the motion made to have the president of the Board of Directors and the medical director members *ex-officio*, that has not been done. Therefore, if this particular recommendation is accepted, so far as the editor of the *Journal* is concerned, it will be for that purpose only, and I should say that the other motion that was passed is out of order.

Dr Bagg replied as follows:

I will state for the information of Dr Bearse and the Council that merely approving of these changes in the by-laws does not make them official. The by-laws state that amendments must be approved by the Council and then submitted with the call to every member of the Society at the annual meeting. It is only at the annual meeting of the Society that by-laws can be changed. But in order to get them in with the Council approval, in the call of the annual meeting, it is necessary to approve them at this meeting. They do not become automatically law. They still have to be ratified by the general body of the members.

Therefore, I would rule that it is not out of order.

Dr Hornor then spoke as follows:

I do not see how we can avoid resubmitting this question to the Council in its May meeting and at the same time having it published in the call for the annual meeting, and as I interpret the by-laws, if the Council at the meeting in May approves of these proposed changes in the by-laws, at the annual meeting they can be approved, accepted or declined.

I therefore think that we should accept the report of the Committee on Publications and also that it would be in order after that report is accepted to submit the changes in by-laws, as we want to have them at the next meeting of the Council, appear in writing to the Council.

All amendments must be submitted in writing, as this one has. And if we can accept Dr Smith's report, I should like to submit the exact form of the changes and by-laws.

that we want to have made and have those published in the call of the May Council meeting and then go to the annual meeting

Dr. Smith moved that the recommendation be approved and the report accepted. The motion was seconded, and it was so ordered by vote of the Council.

*Committee on Arrangements* — Dr. George G. Bailey, Jr., *Chairman*

This report was presented by the Chairman, Dr. Bailey, as follows:

The Committee on Arrangements reports that plans for the program of the 1948 annual meeting are well under way. It expects to present a well balanced program with interesting speakers who will appeal to the membership of the Society.

Our technical-exhibit spaces have as usual all been sold so that the financial success of the meeting is assured but owing to the fact that we have less space available for sale our profits will undoubtedly be less than they have been in recent years.

Special emphasis is being placed upon the scientific exhibits this year and ten hospitals have been invited to present exhibits. These should be a particularly attractive feature of the meeting.

May 25, 26 and 27 are the dates for the meeting with the Council meeting on Monday evening May 24.

Dr. Bagg stated that he had been able to obtain Mary Ellen Chase, of Smith College, as a speaker for the annual dinner and that unless there was objection he would let the committee report stand as printed.

*Committee on Finance* — Dr. Robert W. Buck, *Chairman*

Dr. Buck moved acceptance of this report (Appendix No. 5) and Dr. Phippen seconded the motion. Dr. Buck then spoke as follows:

The report contains three recommendations. The first one is as follows: The Committee recommends that the appropriation to carry the *New England Journal of Medicine* be increased from \$5000 to \$10,000. As you know the amount that is annually appropriated is usually returned. This recommendation means that we want to appropriate \$10,000 that will not be spent, instead of \$5,000 that will not be spent we hope although if it is necessary that that amount of money should be spent by the *Journal* it will be available as a working fund.

I move the acceptance of the recommendation. The second recommendation is as follows: "The Committee further recommends that the *New England Journal of Medicine* shall return to the Society on December 31 any excess of cash over \$10,000 instead of the present amount of \$6,000 as agreed upon in 1940.

The explanation is again quoted from Dr. Smith. If it is not clear to you perhaps Dr. Smith will explain the implications of this in greater detail.

Dr. Smith then spoke as follows:

Several years ago an arrangement was made with the Finance Committee that at the end of the year the *Journal* should return to the Society whatever funds it had in hand over and above \$6,000. In other words this left us a working capital of \$6,000. At the time that that arrangement was made the budget of the *Journal* was considerably under \$100,000 a year. If you will refer to the report of the Committee this year you will see that that amount is nearly \$250,000 now and a working capital of \$6,000 is rather small.

Last year we returned to the Society \$9,000. This year I am sorry to say we will not be able to return any amount and we had to borrow from the Society \$5,000 which we have returned. If our working capital had been \$10,000 instead of \$6,000 we probably should not have had to borrow money from the Society or if we borrowed at all a very small amount. We are simply asking that the *Journal* be allowed to retain in its fund the sum of \$10,000 at the end of the year instead of the sum of \$6,000 as at present.

Dr. Buck resumed speaking as follows:

The third recommendation of the Committee on Finance is brought about by the discovery that the Society is now liable to taxation. This reads: "The Committee on Finance recommends that the Council authorize the payment of a federal social security and unemployment tax for 1947 amounting to \$507.78 and that provision for such taxation be made in future budgets."

The necessity for this recommendation is apparent from the following communication received by this committee from the treasurer of the Society:

The Internal Revenue Department, Washington, have changed our tax exemption from Code 101 (6) to 101 (7) which still exempts us from federal income tax as a corporation but makes us liable to both social security taxation and unemployment taxation for employees. I consulted with Mr. Dodge, the Society's lawyer, to see if we should take it lying down and he said: "Yes, as the only alternative would be to contest it in court with little prospect of winning."

There seems to be no alternative to accepting this change. I move that this recommendation be adopted.

*Committee on Cancer* — Dr. Shields Warren, Suffolk, *Chairman*

Dr. Warren spoke as follows regarding this report (Appendix No. 6):

You have all had the report in the circular of advance information and therefore I shall not read it to you but simply call your attention to the three recommendations made.

I will remind you that at the October meeting of the Council the report of the Committee on Cancer was not accepted but was by vote of the Council placed on the table.

The first recommendation, therefore, is that the report of the committee presented at the October meeting of the Council be taken from the table. I move that this recommendation be adopted.

Dr. O'Hara seconded the motion, and it was so voted.

Dr. Warren then moved that both reports be accepted by the Council. Dr. Phippen seconded this motion, and it was so voted unanimously.

Dr. Warren moved that the Council approve in principle the establishment of a Cancer Detection Clinic at the Palmer Memorial Hospital.

Dr. Bagnall seconded the motion, and it was so voted.

Dr. Warren moved the acceptance of the report as a whole. Dr. Hornor seconded the motion, and it was so voted unanimously.

*Committee on Postwar Loan Fund* — Dr. George L. Schadt, Hampden, *Chairman*

The report of this committee, which is as follows, was presented by Dr. Eliot Hubbard, in the absence of Dr. Schadt:

The Post War Loan Fund was activated by vote of the Council in October 1945. Thirty-five loans have been

made, four of which were renewals of the original loan. The last loan was made on October 30, 1947. The total amount of the loans was \$17,500.

The Committee is of the opinion that the purpose of the Post War Loan Fund has been accomplished and the need for its existence is no longer evident. The Committee, therefore, recommends that the activities of the Post War Loan Fund be discontinued, and that the Committee be discharged.

Dr Hubbard moved the acceptance of the report.

Dr Ober seconded the motion, and it was so voted.

Dr Hubbard moved the adoption of the recommendation that the committee be discharged. Dr Bagnall seconded the motion, and it was so ordered by vote of the Council.

#### *Advisory Committee on Malpractice Insurance — Dr Carl Bearse, Norfolk, Chairman*

This report was presented by the Chairman, Dr Bearse, as follows:

The Advisory Committee on Malpractice Insurance appointed by the Council to "serve in an advisory capacity to the Society and insurance companies in regard to malpractice suits" has held two meetings. The function and scope of this committee were discussed. It was voted that all members of the Massachusetts Medical Society be urged to carry malpractice insurance (the Society has no funds for payment of verdicts or for expert medical testimony for those members not insured), and that all insurance companies writing malpractice insurance in Massachusetts be notified regarding the existence of this committee and of its desire to co-operate with them. It was also recommended that these companies be asked to furnish this committee with answers to the following questions:

How many suits are actually brought into court each year and what is the disposition of these suits? (Names of physicians involved will not have to be given.) The committee is considering the advisability of having "listeners" at these trials and would like to know how often this might be necessary.

Is it their belief that this committee could be helpful in the selection of experts to testify at suits for malpractice?

Would they desire to have this committee review the testimony of physicians who have testified in a manner that appears to them to be below the standards applicable to members of the Massachusetts Medical Society?

Dr Bearse continued as follows:

This is the first report of a new committee. This committee came into being at the previous Council meeting. Its function is to serve in an advisory capacity to the Society and to insurance companies regarding malpractice suits.

The committee believed that since it is new and its duties are not clearly defined, it should proceed slowly and with caution. No action as yet has been taken. No letters have been sent. We have delayed taking any steps until this report has been acted upon.

The committee believes that all members of the Society should be urged to carry malpractice insurance. The Society has no funds for the payment of damages awarded or for expert medical testimony for members who are not insured.

The committee also believes that the insurance companies writing malpractice insurance in the Commonwealth should be notified regarding the existence of this committee and of its desire to co-operate with them and that these companies should be asked to furnish the committee with answers to the questions asked above. A previous committee, the Committee to Survey the Malpractice Situation in the Commonwealth, tried to obtain the answers to these questions from insurance companies, but without success.

The committee thought it would be helpful to them if they knew how many suits are actually brought into court a year, and what is the disposition of these suits. Names of physicians are not wanted, merely the number and the amounts of money involved.

We should also inform the insurance companies that the committee is considering the advisability of having listeners at these trials and would like to know how often this might be necessary. Incidentally, this was a suggestion made by one of the insurance companies to which we wrote during the course of the survey.

The committee would like to know from the insurance companies whether it could be helpful in the selection of experts to testify at suits for malpractice and also whether the insurance companies would like to have the committee review the testimony of physicians who have testified in a manner that appears to them to be below standards applicable to members of the Massachusetts Medical Society.

Dr Bearse moved the acceptance of the report. Dr Bagnall seconded the motion, and it was so voted.

#### *Report of the Committee of Seven — Dr Reginald Fitz, Suffolk, Chairman*

Dr Fitz pointed out that the report (Appendix No. 7) was divided into two parts, the first recommending that a secretary who devotes his entire time to the work of the Society be henceforth employed. Dr Fitz moved the adoption of that part of the report. Dr Ober seconded the motion, and the Council voted it unanimously.

Dr Fitz stated that the second part of the report dealt with certain suggested amendments to the by-laws and stated that the committee would like to make an amendment by deleting the word "standing" and substituting therefor the word "other."

Dr Fitz stated the committee recommended the acceptance of this part of the report, as so amended.

Dr Bagnall seconded the motion, and it was so ordered by vote of the Council.

Dr Fitz moved the acceptance of the report as a whole. Dr O'Hara seconded the motion, and it was so voted unanimously.

Dr Fitz moved that the committee be discharged. Dr Bagnall seconded the motion, and it was so voted.

#### *Committee on Public Health — Dr Roy J Ward, Worcester, Chairman*

This report, which is as follows, was presented by the chairman, Dr Ward:

The first meeting of this committee was held on September 24, 1947.

The committee approved the inclusion in the State Public Health Nurses' Manual of the use of DDT as one of the recommended methods of treatment of pediculosis capitis. Approval of the committee had been requested by Dr Vlado Getting, commissioner of Health of Massachusetts, prior to publication of a new manual for Public Health Nurses.

The committee also indorsed a proposed change in the present law requiring annual examination of school children. The following motion was adopted: "That this committee approves of a change in the present law and indorses the principle that such examinations be at intervals as may be determined by the Department of Public Health after consultation with the Department of Education."

The problems of increasing pollution of inland and coastal waters were discussed at length by Dr Vlado A. Getting, Dr John E. Gordon and Mr Arthur Weston State Sanitary Engineer. It was noted that the Society has given little attention to this problem for several years and it was voted to request the Committee on Arrangements for the Annual Meeting and the Committee on Postgraduate Education to consider the inclusion of this subject in their programs.

A study is being made of the adequacy of the teaching of public health in medical schools.

It is planned to discuss accident prevention at a future meeting.

Dr Ward stated the report was informational and moved that it be accepted. Dr Phippen seconded the motion, and it was so voted.

*Committee on Postgraduate Assembly*—Dr Leroy E. Parkins, Suffolk, Chairman

The report of the committee is as follows:

On October 29, 30 and 31, 1947, the Sixth Annual New England Postgraduate Assembly was presented with the co-operation of the other state medical societies of New England. The other societies were represented on the Executive Committee by the following: Maine, Dr Fred Erick T. Hill, New Hampshire, Dr John P. Bowler, Vermont, Dr Philip K. Wheeler, Rhode Island, Dr Emory M. Porter, Connecticut, Dr Stanley Weld. A fine spirit of co-operation and helpfulness was evidenced at all times from these representatives in making the Assembly a success.

The program was published in the *New England Journal of Medicine*, issue of October 23, 1947. The committee wishes to express high praise and appreciation of the distinguished group of speakers, who contributed to making the program one of the best that has been presented.

In addition to the usual didactic lectures, clinics in Boston hospitals were held. This was an experiment that was generally very successful so that it will be continued as a feature of the program next year.

All committees of the Assembly deserve the thanks of the Society, also we wish to express our thanks to Mr Boyd who handled the details of business management.

The attendance of physicians for 1947 was 744 (for 1946, 488). The income from booths was \$3,045 and that from registration was \$2,546; the total income was \$5,591. The total expenses as of December 1, 1947, were \$4,917.82. The net profit was \$673.18.

On account of the necessity of reserving hotel space a year or more in advance to ensure choice of dates, the committee makes the following recommendation that a New England Postgraduate Assembly be held in 1948, 1949 and 1950 on the present basis of organization or until such time as the respective societies vote changes and that the dates for the 1948 meeting be November 3, 4 and 5.

Dr Parkins moved acceptance of the report. Dr Bearse seconded the motion, and it was so voted unanimously.

Dr Parkins stated that there was one recommendation that the Assembly be held in 1948, 1949 and 1950 on the present basis of organization or until such time as the respective states vote changes, and that the dates for the 1948 meeting be November 3, 4 and 5. Dr Parkins moved the adoption of this recommendation. Dr Richard M. Smith seconded the motion, and it was so voted.

*Committee on Legislation*—Dr George R. Dunlop, Worcester, Chairman

Dr Dunlop presented the report of the committee, as follows:

At its last meeting on October 1, special powers were again delegated to the Executive Committee of the Committee on Legislation. Mr Charles Dunn was reappointed as legislative counsel. It was voted to submit a budget of \$5,000 to the Committee on Finance.

Dr Dunlop called attention to a bill (H 104) submitted by the Massachusetts Department of Health that he considered important. In 1946 the Hospital Survey and Construction Act became federal law, and under it each state is required to delegate an agent to conduct a survey of the state's needs. To date forty-one states have passed legislation designating the agent. All but nine have designated the state department of health. H 104 designates the department of health as the agent. From a questionnaire sent to all state governors, United States Senator Smith found that Utah was the only state favoring the Wagner-Murray-Dingell Bill.

Dr Dunlop moved acceptance of his committee's informational report.

Dr Lester M. Felton, Worcester, asked if the Committee on Legislation favored H 104. Dr Dunlop said that the executive committee of the committee favored the bill.

Dr Butler pointed out that the Wagner-Murray-Dingell Bill also provides for grants in aid to states initiating health programs.

Dr Bagg requested Dr Conlin to say something about the Nolen-Miles Pound Bill (S 264).

Dr Conlin stated that there were six anti-vivisection bills to be acted upon this year. Material on S 264 appeared in the *New England Journal of Medicine*, issue of February 12. Material is being mailed to the speakers' bureau in eighteen districts, to the Women's Auxiliaries and to the press. The supply of animals is growing increasingly smaller, and this situation has become so acute that the bill is introduced with an emergency preamble to make it possible to obtain more animals at once.

Dr Conlin stressed the importance of unanimity among the members of the Society in this matter and stated that he wished to offer a resolution.

Dr Bagg brought up the point that since the resolution was not in the committee report, the rules would have to be suspended by vote of the Council before action could be taken.

It was so moved and seconded and voted unanimously to suspend the rules. Dr Conlin then introduced the following resolution:

Whereas benefits of inestimable importance have derived from animal experimentation of value to both men and animals; and Whereas the continuation of animal experimentation is a matter fundamental to teaching and research in the medical sciences; Be it resolved by the members of the Council of the Massachusetts Medical Society assembled in Boston on February 4, 1948, that all efforts to restrict humane animal experimentation will be opposed and efforts to make animals from public pounds available for medical teaching and research will be given the strongest possible support.

Dr Bagnall seconded the motion, and it was voted unanimously, followed by applause.

Dr Dunlop moved acceptance of the report Dr Fitz seconded the motion, and it was so voted

Dr Bagg asked the Secretary to read a communication from the chief medical officer of the regional office of the Veterans Administration to Dr Humphrey L McCarthy, chairman of the Committee on Veterans Affairs, under suspension of the rules Dr Gallupe read the letter (Appendix No 8)

Dr Fitz moved that this letter be accepted as the report of the committee Dr Bagnall seconded the motion, and it was so voted

Dr Ober moved to remove the suspension of the rules The motion was seconded and it was so voted

### NEW BUSINESS

Dr Bagg stated that the Executive Committee voted to approve Dr Kickham's motion to refer matters similar to the Gallupe Plan to the Committee to meet with the Massachusetts Hospital Association.

Dr Bagnall moved to approve the motion The motion was seconded, and it was so ordered by vote of the Council

Dr Bagg said that he had received a letter from Dr Howard B Sprague, president of the New England Heart Association, asking for approval of the campaign of the National Heart Association by the Council, the Executive Committee had voted approval

Dr Hornor moved that the Council approve the campaign Dr Fitz seconded the motion, and it was so voted

Dr Bagg stated that the same letter requested a contribution from the Society and that the Executive Committee had voted to take no action on the request

Dr Fitz moved that the Council approve the action of the Executive Committee Dr Bagnall seconded the motion, and it was so voted

Dr Bagg said that Dr Sisson had written a letter to him indicating that news releases from studies on child health care in the United States might be food for thought for the Society, that Dr Curley had moved that the matter be referred to the Committee on Medical Education and that the Executive Committee had so voted

Dr Sisson moved that the Council approve this action Dr O'Hara seconded the motion, and it was so ordered by vote of the Council

Dr Ohler, Norfolk, recalled to members of the Council that, as a part of its wartime activities, the management of the Bureau of Clinical Information had been given to the Committee on Postgraduate Medical Education That committee now recommended that control of the Bureau be taken over by the Secretary as an integral part of the central office of the Society

Dr Bagg stated that under the rules he would refer the matter to the Executive Committee for action at the next meeting of the Council

Approval of this action was moved and seconded and so ordered by vote of the Council

Dr Bagg then said that Dr Getting wished to introduce a resolution Dr Vlado A Getting, Middlesex South, spoke as follows

Because of the urgency required in acting upon this resolution, the Massachusetts Department of Public Health and the American Red Cross have not been able to bring this matter to the attention of the Society in the usual manner This morning I had a conference with Dr Diamond, who is the new technical director of the American Red Cross and who has just returned from Washington

As you know, for the past two years the Department of Public Health has been conducting a program for the free distribution of whole blood and blood fractions to the people of the Commonwealth In June, 1947, the American Red Cross voted on and adopted a policy of making such products available to all the people of the nation

After repeated conferences, including representatives of the American Red Cross and the Commonwealth, and after clearance with the Governor and other officials, it has been the determination of the Department of Public Health that the best policy to adopt in Massachusetts was not to continue this program from tax funds, as we have in the past, which would involve an annual expenditure of between one-quarter and one-half million dollars, but to take this responsibility to the Red Cross and request the Red Cross to assume the responsibility for continuing the Massachusetts blood program

This will mean that our laboratory will still continue and will probably be used by the American Red Cross as a research center, and as a center for processing of some fractions It is hoped that on or about March 1 and certainly by July 1, the collection, distribution and processing of whole blood will become a responsibility of the American Red Cross, provided, however, that the Massachusetts Medical Society endorses in principle this transfer

I, therefore, suggest the following motion

I recommend that the Massachusetts Medical Society approve in principle the transfer of the program for the provision of whole blood and blood fractions from the Massachusetts Department of Public Health to the American Red Cross, with the understanding that this Society and the Massachusetts Department of Public Health will serve in an advisory and consultative capacity to the American National Red Cross in this program

Dr Getting then moved for suspension of the rules to have a vote on the recommendation Dr Bagnall seconded the motion

The President then stated that Dr Ohler's motion was urgent, and that if permitted he wished to include Dr Ohler's resolution under suspension of the rules

The motion to suspend the rules was so voted unanimously

Dr O'Hare, Suffolk, suggested to Dr Getting that his resolution ought to read "approved by the Council of the Society"

Dr Getting accepted the suggestion and moved acceptance of the resolution Dr Ober seconded the motion, and it was so voted

Dr Bagg then asked for approval of Dr Ohler's resolution It was so voted by the Council

Dr Ober, Suffolk, offered the following motion

a) that a committee of five be appointed by the president of the Society to study the recommendations of the Fee Committee, first, with regard to aid to physicians

who are incapacitated through no fault of their own, and second the assisting of widows and orphans of physicians.

b) that this committee present a working plan or plans to this Council, which will implement the recommendations of the Fee Committee.

The motion was seconded, and it was so ordered by vote of the Council.

Dr David Halbersteden, Norfolk, then spoke.

Because of the passage by the Council last fall or the adoption of the report of the McKittick committee and also because of the apparent failure of the Blue Cross to include recommendations in the contract currently under discussion I wish to present two resolutions for consideration and for action under suspension of the rules. The first resolution is as follows:

Whereas the Council of the Massachusetts Medical Society is concerned with the provision now and in the future of the best possible medical care of the people of the Commonwealth and believes that the recommendations of its special committee (sometimes referred to as the McKittick Committee) in avoiding exploitation of the patient, the hospital or the physician is an important factor in the provision of such care, be it Resolved that the Council advise the staff members of hospitals within the Commonwealth to discuss and arrange with the directors and trustees of such hospitals the best ways for promptly carrying out the aforementioned recommendations and that copies of this resolution and of the part of the McKittick Committee be promptly transmitted to the trustees of the Massachusetts Hospital Association and to the directors of the hospitals of the Commonwealth.

After Dr Bagg had said that he thought the matter had already been covered by previous action, the motion was seconded but failed to carry on a show of hands.

Dr Halbersteden then offered the following resolution, for consideration under suspension of the rules.

Whereas the Council of the Massachusetts Medical Society is interested and concerned with the welfare and healthy continuance of the nonprofit insurance plan for hospital care for the people of the Commonwealth, be it Resolved that the Council of the Massachusetts Medical Society suggest to the Directors of Massachusetts Hospital Service, Inc. and to the members of the Massachusetts Hospital Association that this aim can be best achieved by a fair and equitable reimbursement of each and every hospital by a uniform fee for each day of hospital care and by the elimination of payments to any hospital for administration of anesthesia and interpretation of laboratory and x-ray findings because these are professional functions better provided for by insurance for professional services and that.

The Council urge the Directors of the Massachusetts Hospital Service to include these suggestions in the contract currently under consideration and that copies of this resolution be promptly transmitted to the Insurance Commissioner of the Commonwealth, the Trustees of the Massachusetts Hospital Service, Inc., and to the Trustees of the Massachusetts Hospital Association.

Dr Bagg then read a note from the directors of Blue Cross to the effect that although x-ray service and anesthesia will remain in the contract, a differential charge will be allowed for all services to patients in private accommodations.

The motion was seconded.

After discussion by Dr Bagnall and Dr McKittick, Dr McKittick moved that the matter be laid on the table. The motion was seconded, and it was so ordered by vote of the Council.

Dr Ober moved that the rules be suspended. The motion was seconded, and it was so voted.

Dr Bearse moved that the by-laws be amended by the addition of another standing committee, to be known as the Committee on Constitution and By-Laws.

Dr Hornor moved as an amendment that the president of the Society be requested to appoint a committee of three to report to the Executive Committee on what ought to be done about by-laws.

Dr Bearse accepted the amendment.

It was moved and seconded that the matter be laid on the table. On a show of hands the motion to table was carried.

Dr Bagg suggested that a motion to adjourn was in order. The motion was made, seconded and so voted at 110 p m.

H QUIMBY GALLUPE, Secretary

## APPENDIX NO 1

### ATTENDANCE OF COUNCILORS

BARNSTABLE	HAMPDEN
J G Kelley	F H Allen
Berkshire	R L Barrett
Helen M Seville	P E Gear
Bristol North	Fredene Hagler
J V Chagny	F S Hopkins
W E Dawson	A G Rice
M E Johnson	A H Riordan
J L Murphy	J A Scaman
W M Stohhs	G C Steele
	C L Steele
Bristol South	Hampshire
R B Butler	H A Tadgell
J C Cornigan	Middlesex East
William Mason	T P Devlin
C C Tripp	Robert Dutton
Essex North	R W Layton
E S Bagnall	K L MacLachlan
R V Baketel	M J Quinn
G J Connor	R R Stratton
Elizabeth Councilman	Middlesex North
N F DeCesare	R E Cole
H F Fenton	S A Dibbins
A P George	L J Hall
H R Kuth	W F Ryan
P J Look	A J Stewart
R C Norris	Middlesex South
G L Richardson	J M Baty
F W Snow	G F H Bowers
Essex South	Madelaine R Brown
W W Bahson	R N Brown
L F Box	R W Buck
R E Foss	E J Butler
Loring Grimes	J F Casey
C A Herrick	C W Clark
P P Johnson	E A Cooney
B B Mansfield	J G Downing
A E Parkhurst	A G Engelbach
W G Philpen	W C Feeley
H D Stebbins	V A Getting
F E Tivnan	H G Giddings
C F Twomey	H W Godfrey
Franklin	Elot Hubbard Jr
L R Dame	F R Jouett
H M Kemp	

## REPORT OF COMMITTEE ON FINANCE — BUDGET FOR 1948 (Concluded)

		SPECIAL COMMITTEES	
3,750 00	3,369 00	Bureau of Clinical Information	
—	—	Cancer	3,500 00
365 00	357 00	Fee Schedule	50 00
200 00	166 00	Malpractice Insurance Study	50 00
75 00	64 00	Medical Economics	200 00
1,000 00	—	New England Postgraduate Assembly (Income over expenses \$1,016)	—
3,750 00	2,913 00	Postgraduate Education (Income \$2,358)	1,000 00
335 00	181 00	Postwar Loan Fund	3,500 00
—	71 00	Rehabilitation	—
—	30 00	School Medical Services	—
—	361 00	Special Services	75 00
			300 00
		OTHER EXPENDITURES	
4,000 00	4,000 00	Refund to District Medical Societies	8,000 00
100 00	100 00	Dues Council New England State Medical Societies	—
—	5,000 00	To carry <i>New England Journal of Medicine</i>	10,000 00
—	4,233 80	Premium payment pension plan (Mr. Boyd)	4,014 00
—	507 58	Tax expense (Social security and unemployment insurance, newly required by Bureau of Internal Revenue)	670 00
—	—	Contingent fund to cover (approximately) expenses of Director of Medical Information and Education and possible change in salary of Secretary	9,200 00*
\$64,070 00	\$67,220 38		\$86,359 00

\*Amount of Secretary's salary contingent upon possible change to full-time status budget of Director of Medical Information and Education.

†Anticipated expense of delegates to two A. M. A. meetings carries over into 1948, as second meeting was not held until January, 1948.

‡Added expense due to request of A. M. A. for delegates to Cleveland meeting in January, 1948.

§The 1947 budget of the Publications Committee included \$2,000 for publication of directory and \$5,000 to carry *New England Journal of Medicine*. The Committee has requested authority to increase the latter figure to \$10,000.

## ESTIMATED INCOME

Annual dues	1947	1948	(not including \$10 allocation to Bureau of Medical Library)
Non resident dues	\$54,450 00	\$108,900 00	
Censors' fees	2,230 00	2,200 00	
General Fund income	1,250 00	1,250 00	
Committee on Arrangements	5,200 00	5,200 00	
Postgraduate Assembly	6,000 00	4,000 00	
Profit on sale of securities	1,000 00	700 00	
From <i>New England Journal of Medicine</i>	770 00	600 00	
	\$70,900 00	\$122,850 00	

## APPENDIX NO 6

## REPORT OF THE COMMITTEE ON CANCER

A meeting of the committee was held on November 28, 1947.

The problem of cancer-detection clinics in general, and the proposed cancer-detection clinic at the Palmer Memorial Hospital in particular, were discussed. Critical analysis of the functions of a cancer-detection clinic as ordinarily set up shows that the objective of attempting to give the entire population periodic examinations to detect early cancer is impossible, both because of insufficient personnel (for example, it is estimated that it would take all the radiologists in the country a year to give the population a gastrointestinal x-ray series alone) and because of the tremendous cost (over one and a quarter billion dollars a year). Nonetheless, these clinics, largely fostered by lay organizations such as the American Cancer Society and the Donner Foundation, have become tremendously popular and some four hundred are in existence at the present time. At least forty states have clinics of this type.

The American Medical Association and the American College of Surgeons have recognized that there is much of value in these clinics and have laid down certain principles for their establishment and operation. In its recommendation made to the Council at the October meeting the Cancer Committee did not make clear certain important points in which the proposed cancer-detection clinic at the Palmer Memorial Hospital would differ from most of those already established.

This clinic is not planned simply as an addition to the four hundred already established in the country, in spite of the great popular demand for a clinic of this type. It is planned not merely to fulfill the function of finding early cancer in a limited number of patients or of assuring them that they have no sign of the disease. Rather, and far more important, it is aimed primarily at determining procedures of special value in detecting cancer that may be applied by the physician in private practice and at serving as a demonstration center for such procedures.

It is recognized that the best and most effective type of cancer detection should be the work done by the individual practitioner of medicine with his own patients. However, a great number of procedures that might be used in the doctor's office are perhaps not calculated to yield results commensurate with the time, expense and detail involved. The proposed cancer-detection clinic would serve as a proving ground for different types of diagnostic methods and as a center where doctors might come to determine procedures applicable to the problems of their own practice. A number of physicians have neither the time nor the equipment to give the type of examination they consider a person coming to them to determine the presence or absence of cancer should have, and a facility of this type to which they could refer such persons has definite value.

The work of the general practitioners would be augmented by the increased number of cases referred to him for management and treatment. It is desirable that patients accepted by the clinic should be referred by their physicians. In many cases there may be persons who have no family physician and who might therefore be accepted for examination. In all cases, reference for treatment will be made to the physician of the patient's choice.

The relation of such a cancer-detection clinic to the already existing cancer clinics and tumor clinics throughout the Commonwealth has been carefully considered. Since the cancer and tumor clinics are planned for the patient who has a lesion, cancerous or noncancerous, and the cancer-detection clinic is for the person who considers himself well, there can be no conflict. Moreover, the cancer-detection clinic does not attempt therapy in any form.

The question has been raised whether such a clinic might not better be supported in part by voluntary gifts rather than by state or federal funds. This question is an entirely proper one, and it is believed that the support of such a clinic might better come from voluntary gifts if available than from state or federal sources. In the present instance, however, public funds are at hand, and voluntary funds are not. If voluntary funds cannot be readily obtained, public funds should be accepted.

who are incapacitated through no fault of their own, and second the assisting of widows and orphans of physicians b) that this committee present a working plan or plans to this Council, which will implement the recommendations of the Fee Committee

The motion was seconded, and it was so ordered by vote of the Council

Dr David Halbersleben, Norfolk, then spoke

Because of the passage by the Council last fall, or the adoption of the report of the McKittick committee, and also because of the apparent failure of the Blue Cross to include recommendations in the contract currently under discussion I wish to present two resolutions for consideration and for action under suspension of the rules. The first resolution is as follows:

Whereas the Council of the Massachusetts Medical Society is concerned with the provision now and in the future, of the best possible medical care of the people of the Commonwealth and believes that the recommendations of its special committee (sometimes referred to as the McKittick Committee) in avoiding exploitation of the patient, the hospital or the physician is an important factor in the provision of such care be it Resolved that the Council advise the staff members of hospitals within the Commonwealth to discuss and arrange with the directors and trustees of such hospitals the best ways for promptly carrying out the aforementioned recommendations, and that copies of this resolution and of the part of the McKittick Committee be promptly transmitted to the trustees of the Massachusetts Hospital Association and to the directors of the hospitals of the Commonwealth

After Dr Bagg had said that he thought the matter had already been covered by previous action, the motion was seconded but failed to carry on a show of hands

Dr Halbersleben then offered the following resolution, for consideration under suspension of the rules

Whereas the Council of the Massachusetts Medical Society is interested and concerned with the welfare and healthy continuance of the nonprofit insurance plan for hospital care for the people of the Commonwealth be it Resolved that the Council of the Massachusetts Medical Society suggest to the Directors of Massachusetts Hospital Service Inc., and to the members of the Massachusetts Hospital Association that this aim can be best achieved by a fair and equitable reimbursement of each and every hospital by a uniform fee for each day of hospital care and by the elimination of payments to any hospitals for administration of anesthesia and interpretation of laboratory and x-ray findings because these are professional functions better provided for by insurance for professional services and that

The Council urge the Directors of the Massachusetts Hospital Service to include these suggestions in the contract currently under consideration and that copies of this resolution be promptly transmitted to the Insurance Commissioner of the Commonwealth the Trustees of the Massachusetts Hospital Service Inc. and to the Trustees of the Massachusetts Hospital Association

Dr Bagg then read a note from the directors of Blue Cross to the effect that although x-ray service and anesthesia will remain in the contract, a differential charge will be allowed for all services to patients in private accommodations

The motion was seconded

After discussion by Dr Bagnall and Dr McKittick, Dr McKittick moved that the matter be laid on the table. The motion was seconded, and it was so ordered by vote of the Council

Dr Ober moved that the rules be suspended. The motion was seconded, and it was so voted

Dr Bearse moved that the by-laws be amended by the addition of another standing committee, to be known as the Committee on Constitution and By-Laws

Dr Hornor moved as an amendment that the president of the Society be requested to appoint a committee of three to report to the Executive Committee on what ought to be done about by-laws

Dr Bearse accepted the amendment

It was moved and seconded that the matter be laid on the table. On a show of hands the motion to table was carried

Dr Bagg suggested that a motion to adjourn was in order. The motion was made, seconded and so voted at 1 10 p m

H QUIMBY GALLUPE, Secretary

## APPENDIX NO 1

### ATTENDANCE OF COUNCILORS

BARNSTABLE	HAMPDEN
J G Kelly	F H Allen
Berkshire	R L Barrett
Helen M Seville	P E Gear
Bristol North	Fredene Hagler
J V Chagnon	F S Hopkins
W E Dawson	A G Rice
M E Johnson	A H Riordan
J L Murphy	J A Seaman
W M Stobbs	G C Steele
	C L Steele
Bristol South	Hampshire
R B Butler	H A Tadgell
J C Corrigan	
William Mason	Middlesex East
C C Trapp	T P Devlin
Essex North	Robert Dutton
E S Bagnall	R W Layton
R V Baketel	K L MacLachan
G J Connor	M J Quinn
Elizabeth Councilman	R R Stratton
N F DeCesare	
H F Fenton	Minolsex North
A P George	R E Cole
H R Karth	S A Dillibios
P J Look	L J Hall
R C Norris	A F Ryan
G L Richardson	W J Stewart
F W Snow	
Essex South	Middlesex South
W W Babson	J M Bary
L F Box	G F H Bowers
R E Foss	Madeline R Brown
Loring Grimes	R N Brown
C A Hernek	R W Buck
P P Johnson	E J Butler
B B Mansfield	J F Casey
A E Parkhorst	C W Clark
W G Philpen	F A Cooney
H D Stebbins	J G Downing
P L Tivnan	A G Engelbach
C F Twomey	W C Feeley
Franklin	V A Getting
L R Dame	H G Oldings
H M Kemp	H W Godfrey
	Ehot Hubbard, Jr
	F R Jouett



A A Levi  
R A McCarthy  
J H McSweeney  
Dudley Merrill  
Dwight O'Hara  
Fabyan Packard  
G A Saunders  
M J Schlesinger  
A B Toppan  
J B Townsend  
R H Wells  
Hovhannes Zovickian

## NORFOLK

B E Barton  
Carl Bearse  
J H Cauley  
G L Doherty  
Albert Ehrenfried  
J M Faulkner  
Susannah Friedman  
D L Halbersleben  
J B Hall  
H B Harris  
R J Heffernan  
P J Jakmauh  
C J Kickham  
C J E Kickham  
D L Lionberger  
D S Luce  
C M Lydon  
T F P Lyons  
R L Mason  
F P McCarthy  
H L McCarthy  
R T Monroe  
H R Morrison  
D J Mullane  
H A Novack  
W R Ohler  
R S Palmer  
G W Papen  
H A Rice  
S A Robins  
D D Scannell  
J A Seth  
L A Sieracki  
S L Skvirsky  
E C Smith  
Kathleen Snow  
J W Spellman  
W J Walton  
N A Welch  
Marjorie Woodman  
E T Wyman

## NORFOLK SOUTH

D L Belding  
W R Helfrich  
Frederick Hinchliffe  
E K Jenkins  
N R Pillsbury  
D B Reardon  
H A Robinson  
R G Vinal

## PLYMOUTH

J C Angley  
A L Duncombe  
P H Leavitt  
C D McCann

## SUFFOLK

H L Albright  
W J Bricklev  
W A Browne  
A J A Campbell  
M Henry Clifford  
A P Derhagopian  
N W Faxon  
Reginald Fitz  
M Fremont-Smith  
Channing Frothingham  
G L Gately  
John Homans  
A A Hornor  
L M Hurxthal  
H A Kelly  
T H Lanman  
Roger I Lee  
C F Maraldi  
F W Marlow, Jr  
L S McKittrick  
Donald Munro  
F R Ober  
J P O'Harc  
L E Parkins  
L E Phaneuf  
J J Regan  
W H Robcy  
Horatio Rogers  
H F Root  
R M Smith  
C M Stearns  
Augustus Thorndike  
Conrad Wesselhoeft

## WORCESTER

A W Atwood  
F T Bousquet  
F B Carr  
G R Dunlop  
W J Elliott  
John Fallon  
L M Felton  
R H Goodale  
D K McClusky  
J M Olson  
F A O'Toole  
E L Richmond  
N S Scarcello  
R F Sullivan  
J J Tegelberg  
R J Ward  
B C Wheeler

## WORCESTER NORTH

J J Curley  
C B Gay  
J C Hales  
C S McPeak  
J V McHugh

President Bagg presented Dr Channing Frothingham, a former president of the Massachusetts Medical Society, who was present at Dr Bagg's invitation to speak on the National Physicians Committee, inasmuch as he had not been given an opportunity to do so at the last meeting of the Council

The discussion regarding the National Physicians Committee arose in consequence of the fact that the Committee on Public Relations, at its last meeting, recorded itself as approving the objectives of this committee. Dr Daniel B Reardon and Dr John F Conlin stated that they had been present at the September meeting of the National Physicians Committee and were very favorably impressed with the work of this committee, especially by the factual presentations and discussions and the absence of high-pressure salesmanship. It was stated that there were two different groups

One group received its financial support mostly from physicians and concerned itself entirely with medical problems, particularly with socialized medicine as it manifested itself in the Wagner-Murray-Dingell Bill

The second group was mainly supported by institutional grants and was interested chiefly in educational and research problems, such as the communistic influences in educational and political structure

It is the opinion of the National Physicians Committee that socialized medicine could be the keystone for a communistic state. Drs Reardon and Conlin believed that the objectives of the National Physicians Committee could be approved so far as this committee concentrated its effort in the defeat of the Wagner-Murray-Dingell Bill

It was Dr Frothingham's contention that many of the facts presented by the National Physicians Committee were erroneous and debatable, and that the true facts concerning this committee should be presented to the members of the Council before any final action could be taken concerning the endorsement by the Council of the objectives of this committee

Dr Howard Root, Suffolk, made a motion that Drs Conlin, Reardon and Frothingham meet with the Committee on Medical Economics and present to the next meeting of the Council facts concerning the National Physicians Committee, presenting such arguments, for and against the controversial issues, as may arise with reference to the work and objectives of this Committee

Dr Conlin emphasized the necessity of some directive by the Massachusetts Medical Society about the attitude of the Society toward the National Physicians Committee, inasmuch as he has been constantly questioned

The motion was carried

Dr N S Scarcello's resolution, which had been sent back to the Public Relations Committee by the Council (namely "That the Blue Shield, through its employees, determine accurately an applicant's yearly earnings before issuing a policy, and secondly, that these earnings be reviewed each year") was returned to Dr Charles D McCann's Subcommittee on Blue Cross-Blue Shield Problems

Dr S A Dibbins, Middlesex North, stated that in Lowell patients hospitalized because of diagnostic problems could not have their bills paid as members of the Blue Cross, but the same patients, if they were admitted to the Pratt Diagnostic Clinic, had their bills paid by the Blue Cross

It was suggested by President Bagg that this criticism of the Blue Cross be sent to Dr Charles D McCann's special subcommittee for further investigation

Dr N S Scarcello, Worcester, expressed the opinion that the members of the Massachusetts Medical Society were not adequately informed concerning the financial status of the Blue Shield inasmuch as the members are responsible and liable for this corporation. President Bagg agreed with Dr Scarcello's opinion and requested Dr Scarcello to notify him personally, in writing, to this effect

The following letters were received by the Secretary and were presented merely as matters of information. From Dr Brendan D Leahey, secretary of Middlesex North District Medical Society, the following

At the last meeting of the Middlesex North District Medical Society, there was considerable discussion of Blue Shield fees. Many of the members resented the fact that the Blue Cross rates to the subscriber were raised to allow greater payments to the hospitals but the Blue Shield

## APPENDIX NO 2

## REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

A meeting of the committee was held on November 12, 1947. In addition to representatives of nine district societies the following were present: President Edward P Bagg, who acted as chairman of the Committee, Dr Daniel B Reardon, president-elect, Dr H Quimby Gallupe, secretary of the Society, Dr John F Conlin, Director of Medical Education and Information, and Mr Robert St B Boyd, executive secretary

rates were left unchanged. It was unanimously voted that "The Middlesex North District Society shall go on record as favoring an increase to the basic rates of the Blue Shield paralleling that of the Blue Cross so that payments to physicians may be increased."

This action is to be brought to the attention of the Executive Committee of the Massachusetts Medical Society. It was also suggested that all other district societies be informed of our views in this matter with the hope that they will discuss the situation and take appropriate action.

A letter from Dr. Bernard Appel, Essex South, was then read, stating that the medical staff of the Salem Hospital was unanimously opposed to the inclusion of professional services in the Blue Cross policy.

Dr. Appel wished that this information be conveyed to the special Subcommittee on Blue Cross-Blue Shield Problems. These matters were turned over to Dr. McCann's special Subcommittee on Blue Cross-Blue Shield Problems.

Dr. John F. Conlin gave a general summary of the work of the Director of Medical Education and Information. He stressed the value of public relations to the individual physicians as well as to society at large. He discussed the occasional necessity of accepting invitations to speak to various groups in the districts and believed that courtesy clearances could be obtained from the local public relations councilor or the district officers that the district could be kept informed of his local speaking engagements. He furthermore stressed the importance of his liaison professional activities with various groups, especially the legal group, and mentioned the advisability of joint meetings at state level such as those being held at the Malden Hospital and under the auspices of the Suffolk District Medical Society.

He reported as having given a talk on interprofessional co-operation to the Metropolitan District Dental Society and stated that talks of a similar nature are being booked with nurses, optometrists and chiropractors. These discussions are bringing an excellent response and improved public relations.

'Career Day,' as sponsored by the Exchange Club of Needham for the students of the Needham High School was reported. At that time a general report on the choice of a career was given all students. A number of professional men and representatives from business, trade, industry and so forth presented the pros and cons of their occupations to groups of students. Dr. Conlin presented medicine and was impressed by the interest and questions of the students.

There was also reported numerous appearances by Dr. Conlin before various commissions and State House committees. He stated that there was a marked interest in education in health and in the attitude toward health examinations in school. Joint conferences are being planned with school superintendents, teachers, health educators and school physicians.

With reference to the radio programs Dr. Conlin mentioned the Saturday morning program given at 11:30 for half an hour by five Boston hospitals, 'Medical Center of the Air,' which was given with Society approval.

The new program, 'Doctor's Orders,' which is being given at 1:15 p.m. on Sundays with combined dramatizations and pertinent physician interviews is going over quite well. Scripts have been furnished for two of these six monthly broadcasts over WHAV in Haverhill. A new series of scripts slanted at the animal-experimentation background of medical research is now in hand.

Press releases are being planned to keep the public informed of the Society's interest in health and health education. Newsletters are very much desired to keep all the members of the Society informed concerning legislative matters and other activities of the Society. This goes a long way toward building better and stronger internal relations, which are so necessary to satisfactory public relations.

It is furthermore hoped by Dr. Conlin to arrange several public forums about six in number on medical topics. These are to be presented in Greater Boston and without charge as a public service feature. If hall and speaker co-operation can be obtained.

Dr. Conlin further reported that the Society headquarters facilities are being used to an increasing extent by members

seeking information. Requests for speakers are increasing and the Speakers' Bureau is making slow but favorable progress.

Better Business Bureaus are showing interest in ethical advertising practices pertaining to medicine.

With reference to the Women's Auxiliaries, Dr. Conlin reported that Norfolk and Suffolk districts are organized with other districts as Essex South and Middlesex South in the process of organizing.

Mention was also made by the Director of Medical Education and Information that a number of physicians, many of them graduates of approved schools, were unable to obtain hospital-staff appointments. A few complaints have been received from veteran physicians experiencing difficulty in returning to appointments previously held. The matter is under study and survey data will be accumulated.

Dr. Conlin also received the following letter from the Massachusetts State Nurses Association:

One of the current activities of the Massachusetts State Nurses Association through its public relations committee is the preparation of a Fact Sheet on schools of nursing in Massachusetts. The material is ready to go to the printer.

The recruitment of students for schools of nursing is an interest of other groups as well as of the nursing organization. Already the Massachusetts Hospital Association and the Massachusetts League of Nursing Education have endorsed the Fact Sheet and are helping to underwrite a portion of the cost. We feel the Massachusetts Medical Society also might be interested to a similar extent and make available to its members the Fact Sheet for information and distribution. For it is a known fact that young women turn to their family physician for advice about nursing schools.

The estimated cost for printing 10,000 copies of the Fact Sheet is \$200. Would the Massachusetts Medical Society consider \$50 toward the cost of printing?

We would appreciate a favorable consideration of this matter that we might include the name of the Massachusetts Medical Society with the other organizations as publishers of the Fact Sheet.

HELEN G. LEE, Executive Secretary

The Committee on Public Relations recommended the expenditure of the \$50.

Dr. Conlin again emphasized his willingness to co-operate with the district societies in initiating the women's auxiliary groups.

President Bagg stated the request of Former President Elmer Bagnall that this committee express an opinion about taking out additional subscriptions of the Marjorie Shearon Medical Legislative Service in Washington. This would necessitate an increase of the subscription fee from \$200 to \$500. This received the endorsement of the Committee on Public Relations with the request that the members of the committee receive a copy of the Service.

This report was approved.

The meeting was adjourned at 7:00 p.m.

HAROLD R. KURTZ, Secretary

## APPENDIX NO. 3

### NATIONAL PHYSICIANS' COMMITTEE

The National Physicians Committee was organized in 1939 as a nonprofit organization to speak for the American Medical Association in an interim if a court decision was unfavorable. After the litigation in the Washington case died down it was the opinion that such an organization outside organized medicine could do many things in the field of public education and legislative representation that might be helpful.

The principal object of the National Physicians Committee is to bring about an appreciation on the part of the general public of the outstanding medical care that has been received under the private practice system and by all means to emphasize that particular point.

The National Physicians Committee is like a public relations councilor employed to educate the general public. It has succeeded in bringing about a realization that if medicine and the administration of health care services are

brought under federal control, it will be only a short step until all business will be directly controlled by the federal Government

The policies of the National Physicians Committee are decided by a board of trustees well known to the medical profession. At the centennial meeting of the American Medical Association a reference committee gave final recommendation to the efforts of the National Physicians Committee in spite of the fact that the American Medical Association itself had expanded its public-relations program.

Through the efforts of the National Physicians Committee on a go-ahead from the American Medical Association the little Wagner-Murray-Dingell Bill in Hawaii has been defeated during the past year.

The National Physicians Committee was active during the Seventy-Ninth Congress, and twenty-seven out of thirty-five volumes of testimony on the health-service bill include attacks on the National Physicians Committee by those most interested in the passage of the compulsory health legislation.

The National Physicians Committee does not maintain that all those in favor of compulsory health insurance are communists or belong to the Communist Party, but it does maintain that socialization of health care services is the keystone of the socialized state.

In the coming hearings the National Physicians Committee has arranged to have Dr. Friedman available for consultation with physician witnesses, and Miss Elizabeth Wilson, of Boston, an expert actuary, will be available as a technical adviser.

## APPENDIX NO 4

### REPORT OF THE EXECUTIVE COMMITTEE

The Executive Committee of the Council met on January 7, 1948, in Sprague Hall, 8 Fenway, Boston, Massachusetts, at 4:00 p.m. The meeting was called to order by President Edward P. Bagge. Present were Dr. Daniel B. Reardon, president-elect, Dr. Elton Hubbard, Jr., treasurer, Dr. H. Quimby Gallupe, secretary, and representatives of all district societies except Barnstable, Berkshire, Bristol South, Middlesex South and Suffolk.

The record of the meeting of September 3, 1947, as presented at the meeting of the Council on October 1, 1947, was submitted by the Secretary and was approved.

### COMMITTEE REPORTS

Dr. Bagge presented the matter of the Blue Shield as discussed at the October Council meeting and read a letter from Dr. N. S. Searcello, Worcester, expressing the opinion that members of the Society were not adequately informed concerning the financial status of the Blue Shield. Dr. Curley, Worcester, reported that the Blue Shield has initiated in Worcester County a method by which the participating physicians notify the Blue Shield instead of going through the Blue Cross. The patient initiates the upper part of the notice, and the physician completes it when the patient has left the hospital. It is sent to Blue Shield and the doctor should be paid in ten days or less. The income of the patient is discussed by doctor and patient in the office. Worcester District Medical Society recommends that the fees of general surgery should be increased. Blue Shield has a low administrative cost (8 per cent), ordinary insurance-company costs run to 30 or 40 per cent. Dr. Curley asked whether the subcommittee was running Blue Shield or whether the Executive Committee was running it. Dr. Bagge explained that the Executive Committee is too unwieldy to work on the matter, that he expected the subcommittee to report at the annual meeting, and that the Executive Committee would finally act.

Dr. Curley moved to approve the following changes in the by-laws suggested in a letter from Dr. Bagnall as requested by Dr. Bagge:

"Referring to the by-laws, Chapter IV, Section I, in line 5, strike out the word 'and,' inserting a comma there instead, after the word 'committees' inserting a comma instead of a period, and then adding the following words 'with the Medical Director of the Massachusetts Medical

Service, Inc., and the President of the Massachusetts Medical Service, Inc., if he be a member of the Society."

This motion was seconded by Dr. Wheeler and put to a vote and unanimously carried.

Dr. Bagge then presented Mr. Peterson, representing the National Physicians Committee, who described what the committee had done, what its objectives are, and what had been accomplished so far. Dr. Appel, Essex South, pointed out that no action concerning the approval or disapproval of the work of the National Physicians Committee could be taken because the committee consisting of Drs. Reardon, Conlin and Frothingham had made no report. Dr. Conlin reported that no meeting of that committee had been held. Dr. Bagge then ruled that no action could be taken until that subcommittee reported.

### Committee on Publications

Dr. Dame moved that the report of this committee as published in the circular of advance information be accepted. Dr. Wheeler seconded the motion. The motion was carried.

Dr. Curley moved to sponsor the resolution that the editor of the *Journal* should *ex-officio* be a member of the Council. Dr. Wheeler seconded the motion. The motion was voted unanimously.

Dr. Smith pointed out that the *Journal* this week reached 25,000 copies, the highest in its history.

### Committee on Arrangements

This report was accepted as informational. Dr. Bagge reported that he had obtained Mary Ellen Chase, head of the Department of English literature at Smith College, as the speaker at the annual dinner.

### Committee on Finance

This committee voted unanimously that the salaries of two office employees be increased to \$40 per week retroactive to January 1, 1948. (These words do not appear in the printed report of the committee but the figures in the budget are on line 16, page 13 of the circular of advance information.) The report of this committee was accepted unanimously.

### Committee on Cancer

Dr. Bagge ruled that the report of this committee presented at the October 1 meeting of the Council be taken from the table. Dr. Wheeler so moved. It was seconded and voted.

It was then moved that the first and second reports of the committee be accepted. This motion was voted and carried.

It was then moved and seconded that the Council approve in principle the establishment of a cancer-detection clinic at the Palmer Memorial Hospital. This motion was voted unanimously. It was then moved and seconded that the report as a whole be accepted. The motion was voted and carried unanimously.

### Postwar Loan Fund Committee

Dr. Hubbard moved that the report be accepted and the committee be discharged. Dr. Wheeler seconded the motion, which was voted and carried unanimously.

### Committee on Malpractice Insurance

Dr. Bearse read the report as printed and moved acceptance. Dr. Curley seconded the motion, which was voted and carried.

### Report of the Committee of Seven

Dr. Fitz read and emphasized parts of the report. He also pointed out that on page 20, line 22, the word "standing" should be deleted. Dr. Fitz then moved the acceptance of this report with the one change mentioned above. Dr. Curley seconded the motion, which was voted and carried unanimously.

Dr. Fitz pointed out that the committee had further duties and submitted the following supplementary report:

The committee recommends that a basic salary of \$10,000 a year be accepted as proper for a secretary who devotes his entire time to the work of the Society, such

basic salary to be adjusted from year to year by the Council in such fashion as the Council deems proper.

Under authority granted by the Council at the stated meeting on October 1 1947 the Committee has arranged with Dr. Gallupe, now secretary, to devote as much of his time as possible to the work of this office until his successor is elected. The committee estimates that he will spend at least two thirds of his time for the benefit of the Society between now and the annual meeting. The committee therefore has ordered the Treasurer to pay him from January 1 1948 until the annual meeting at the rate of \$550 per month this figure being approximately two-thirds of the monthly stipend that would be paid to a secretary receiving \$10 000 a year.

Dr. Fitz then moved that the Executive Committee approve the action of the Committee of Seven. Dr. Curley seconded the motion which was carried unanimously.

#### *Report of the Advisory Council to the Women's Auxiliary*

This report was adopted as one of progress.

#### *Committee on Public Health*

This report was adopted as one of progress.

#### *Committee on Postgraduate Assembly*

It was moved and seconded that the recommendation beginning on line 5 page 22 be adopted. The motion was carried.

#### *Committee on Legislation*

This report was adopted as printed.

### NEW BUSINESS

Dr. Charles J. E. Kiekham, Norfolk, stated that the councilors of the Norfolk District Medical Society had voted to request him to move that the Executive Committee approve a new committee on hospital relations to which might be referred matters like the Gallupe Plan. Dr. Bagg suggested that there are now two committees on hospitals. Dr. Appel seconded Dr. Kiekham's motion. Dr. Dame moved to amend the motion to the effect that if the function could be taken care of by a present committee there would be no need of a new committee. Dr. Kiekham stated that he wished to add specifically the relation of the hospital to the Gallupe Plan.

Dr. Bagg then stated the motion as he understood it as follows: "Unless one committee can be found already in existence that a new committee be appointed to further the relations of hospitals to the Society with special attention to the Gallupe Plan."

This motion was seconded, voted and carried.

Dr. Bagg read a letter Dr. Howard Sprague asking for Society endorsement on the campaign of the National Heart Association. It was moved and seconded that such endorsement be recommended to the Council. The motion was carried.

Dr. Bagg pointed out that the Society had no authority to appropriate money to any such drive as that of the National Heart Association. It was moved and seconded to take no action on this request.

Dr. Bagg read a letter from Dr. Sisson indicating that news releases from studies on child health care in the United States would be food for thought for the Society. Dr. Curley moved that the matter be referred to the Committee on Medical Education. The motion was carried.

The meeting was adjourned at 6:15 p.m.

H. QUIMBY GALLUPE, Secretary

## APPENDIX NO 5

### REPORT OF THE COMMITTEE ON FINANCE

The committee met December 3 1947 to consider the budget of the Society for the year 1948. The budget agreed upon is presented herewith. The figures for expenditures during 1947 are only approximate being based upon the

Treasurer's records for the first ten months of the year. In addition to estimates for the remaining two months. The major increases and variations are explained in the footnotes. Action by the Council is requested on several of these changes.

The Committee recommends that the appropriation to carry the *New England Journal of Medicine* be increased from \$5 000 to \$10 000.

The following is from a letter received by the committee from the chairman of the Committee on Publications, Dr. Richard M. Smith:

The cost of materials and all other things is constantly rising and we cannot estimate exactly our budget for 1948. To cover emergencies we request an appropriation of \$10 000 from the Society. We hope very much that it will not be necessary to use this money but to be on the safe side we think we shall need the appropriation available for emergencies. We shall probably be able to return to the Society most of the \$5000 of this year's appropriation.

The Committee further recommends that the *New England Journal of Medicine* shall return to the Society on December 31 any excess of cash over \$10 000 instead of the present amount of \$6000 as agreed upon in 1940.

This recommendation is likewise explained by Dr. Smith as follows:

In 1940 it was agreed that at the end of the year if the *Journal* had any surplus cash over and above \$6000 it should be returned to the Society. This meant, in effect, that the budget of the *Journal* had a working capital of \$6000. At that time the total budget of the *Journal* was very much less than at the present time and we now are somewhat embarrassed by the small working capital. We therefore ask the Committee on Finance to change the arrangement previously made so that the *Journal* shall return to the Society on December 31 any excess of cash over \$10 000 instead of the present amount of \$6000. Our actual expenses for last year were nearly \$250 000 formerly they were well under \$100 000.

The committee recommends that the Council authorize the payment of a federal social security and unemployment tax for 1947 amounting to \$507.58 and that provision for such taxation be made in future budgets.

The necessity for these recommendations is apparent from the following communication received by the committee from the Treasurer of the Society:

The Internal Revenue Department Washington have changed our tax exemption from Code 101 (6) to 101 (7) which still exempts us from federal income tax as a corporation but makes us liable to both social security taxation and unemployment taxation for employees. I consulted with Mr. Dodge the Society's lawyer to see if we should take it lying down and he said: "Yes as the only alternative would be to contest it in court with little prospect of winning."

The committee has set aside a contingent fund of \$5500 in anticipation of a possible increase in salary for the secretary of the Society in case the Committee of Seven should decide that a full time incumbent be elected (as has been proposed) and to cover as well the expenses of the new Bureau of Medical Information and Education. The Committee on Finance is unable to set any exact figure for these two items since no action has as yet been taken that will definitely establish the amount of money required. Action by the Council will enable these figures to be made definite and will no doubt be requested by the appropriate persons.

An estimate of 1948 income prepared by the Treasurer indicates that the Building Fund may be increased by perhaps \$35 000 this year unless expenditures are greater than anticipated in the budget.

ROBERT W. BLOK, Chairman  
FRANCIS C. HALL  
BRYAN PACKARD  
BACROFT C. WHEELER  
CHARLES F. WILKINSKY

DETAILED EXPENDITURES — 1947

Expenses of Officers, etc.

<i>President</i>	
Meals	\$33 39
Hotel Room	42 35
	<u>75 74</u>
Estimate for November-December	135 26
	<u>211 00</u>
<i>President-Elect</i>	
Transportation January-May	74 00
<i>Secretary</i>	
Supplies	97 94
Printing and Engraving	1 515 31
Travel	270 92
Reporting meetings	168 50
Telephone	27 31
Mailing	141 76
Petty cash	117 10
	<u>2,338 84</u>
Estimate for November-December	900 00
	<u>\$3,238 84</u>
<i>Treasurer</i>	
Loomis and Sayles	1,218 72
Rent on box	18 00
Premium on bond	37 50
Hartshorn and Walter	315 00
Petty cash	12 17
Printing	271 95
Supplies	6 95
	<u>1,880 29</u>
Estimate for November-December	68 10
	<u>1,948 39</u>
<i>Director, Medical Information and Education</i>	
Estimate for November-December	110 32
	<u>200 00</u>
	<u>310 32</u>
<i>Delegates to A M A</i>	676 23
<i>Shattuck Lecture</i>	200 00
<i>Cotting Luncheons</i>	450 00
Deduct income Cotting Fund	148 00
	<u>302 00</u>
<i>General Administrative Expense</i>	
Printing	498 55
Supplies	766 31
Clerical from Journal	90 00
Petty cash	237 91
Blue Cross premiums	119 25
Rental of typewriters	17 50
Telephone	488 23
Funeral flowers	35 00
Installation of machines	121 01
Inspection of machines	26 00
Rental of Sprague Hall	10 00
Dues	5 00
Stamps	68 25
Travel Mr. Boyd	81 31
Travel to Chicago	151 16
Subscription to J A M A	8 00
Rental, water cooler	25 35
	<u>2,748 83</u>
Estimate for November-December	194 00
Clerical work for year	5 252 00
	<u>8 194 83</u>
<i>Committees Elected by District Societies</i>	
<i>Executive</i>	
Meals	187 98
Petty cash	37 00
	<u>224 98</u>
Estimate for November-December	00 00
	<u>224 98</u>
<i>Legislation</i>	
Supplies	27 50
Charles Dunn	3,500 00
Mimeographing	58 67
Travel	100 33
Dr. Bagnall to Washington	16 50
Reporting	116 23
Telephone	10 98
Meals	224 09
Petty cash	1 85
Subscriptions	200 00
	<u>4 256 15</u>
Estimate for November-December	68 10
	<u>4 324 25</u>

Public Relations

Meals	155 56
Estimate for November-December	300 00
	<u>455 56</u>
<i>Standing Committees</i>	
<i>Arrangements</i>	
<i>Income</i>	
From booths	\$13 580 00
Tickets to party	144 00
Tickets to Annual Meeting	3,213 85
From Ladies' Committee	145 90
Statler overpayment	29 11
	<u>17,112 86</u>
<i>Expenses</i>	
Golf prizes and Tournament	54 75
Printing	611 57
Telephone	27 52
Meals	374 50
Editing program	35 00
Stationery	73 65
Rental lanterns	147 00
Transportation, speakers	230 67
Badges	177 41
Statler	8,487 97
Erection booths	52 30
Music	55 00
Flowers	15 00
Signs	85 00
Public relations	150 00
Petty cash	24 03
Buses	35 00
	<u>10 656 97</u>
Estimate for November-December	82 00
	<u>10 738 97</u>
<i>Profit</i>	6,373 89
<i>Ethics and Discipline</i>	
Meals	30 25
Legal opinion	20 00
Petty cash	20
	<u>50 45</u>
Estimate for November-December	9 40
	<u>59 85</u>
Less income from Brickley Fund	20 00
	<u>39 85</u>
<i>Finance</i>	
Estimate for November-December	10 00
<i>Industrial Health</i>	
Meals	17 60
<i>Medical Defense</i>	
Legal	846 08
Estimate for November-December	00 00
	<u>846 08</u>
<i>Medical Education</i>	
<i>Membership</i>	
Meals and Room	50 41
Clerical work, State House	25 00
Telegrams	6 89
Telephone	10 92
	<u>93 22</u>
Estimate for November-December	26 83
	<u>120 05</u>
<i>Publications</i>	
Directory, clerical	12 00
Estimate for November-December (Directory)	2 000 00
	<u>2 012 00</u>
<i>Public Health</i>	
Massachusetts Central Health Council dues	10 00
Travel	109 70
Meals	57 01
	<u>156 71</u>
Estimates for November-December	57 75
	<u>214 46</u>
<i>Society Headquarters</i>	
Machines	3,476 75
Electricity	166 15
Cleaning	190 00
Rent	2 437 50
Office equipment	91 00
Carpentry and repairs	109 96
	<u>6 471 36</u>
Estimate for November-December	925.37
	<u>7 396 73</u>

## Special Committees

*Branch of Clinical Information*

Wages	1,806 00
Mimeographing	81 75
Telephone	79 95
Supplies	250 86
Stamps	255 00
Extra clerical	91 80
Petty cash	3 85
	<hr/>
Estimate for November-December	2,569 21
	800 00
	<hr/>
	3,369 21

*Fee Schedule*

Printing	31 39
Telephone	3 92
Travel	189 34
	<hr/>
	224 65
Estimate for November-December	132 00
	<hr/>
	356 65

*Malpractice Insurance Study*

Meals	19 08
Printing	35 35
Petty cash	3 15
Secretarial	110 00
	<hr/>
Estimate for November-December	165 58
	00 00
	<hr/>
	165 58

*Medical Expenses*

Meals	63 54
Estimate for November-December	00 00
	<hr/>
	63 54

*N. E. Postgraduate Assembly*

Income	
Booths	5,005 00
Tickets	2,858 87
	<hr/>
	5,863 87
Expenses	
Meals	18 09
Printing	396 64
Envelopes and addressing	437 44
Refund on rental space	15 00
Petty cash	1 35
Mailing	55 01
Mimeographing	33 50
Badges	85 56
Cash on hand for meeting	50 00
	<hr/>
Estimate for November-December	1,094 59
	3,723 19
	<hr/>
	4,817 78
Profit	1,046 09

## Postgraduate Education

## Income

Sale of tickets Sanders Theater	1,258 25
Payments from Commonwealth of Massachusetts	1,100 00
	<hr/>
	2,358 25

## Expenses

Printing	299 00
Meals and rooms	171 50
Typing	7 00
Mailing	13 93
Lectures and travel	3,027 16
Telephone	11 34
Lunches, Sanders Theater	1,315 30
Set up Sanders Theater	406 43
	<hr/>
Estimate for November-December	5,271 66
	00 00
	<hr/>
	5,271 66

## Less Income

	2,358 25
	<hr/>
	2,913 41

## Net expense

## Partner Loan Fund

1% on 10 loans of \$500	150 00
Telephone	1 12
	<hr/>
	151 12

## Estimate for November-December

	10 00
	<hr/>
	161 12

## Rehabilitation

Meals	1 03
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## School Medical Services

Meals	20 45
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## Special Services

Post cards	10 00
Meals	101 28
	<hr/>
	111 28

## Other Expenditures

Refund to District Medical Societies	4,000 00
Dues Council N. E. State Medical Society	100 00
To carry New England Journal of Medicine	800 00
Premium payments pension plan (Mr. Boyd)	4,334 80
Taxes (social security and unemployment insurance)	50 55

## REPORT OF COMMITTEE ON FINANCE -- BUDGET FOR 1948

Budget 1947	Expenditures 1947		Budget 1948	Change
\$4,000 00	\$4,000 00	<b>SALARIES</b>		
4,800 00	4,800 00	Secretary	Continued*	—
2,500 00	2,500 00	Executive Secretary	4,800 00	—
—	3,750 00	Treasurer	2,500 00	—
		Director Medical Information and Education	8,000 00	+ 8,000 00
		<b>EXPENSES OF OFFICERS, ETC.</b>		
300 00	211 00	President	300 00	—
300 00	74 00	President Elect	100 00	+ 200 00
1,500 00	3,239 00	Secretary	3,500 00	+ 2,000 00
2,000 00	1,948 00	Treasurer	2,000 00	—
—	310 00	Director Medical Information and Education	Continued*	—
1,500 00	676 00	Delegates to A. M. A.	1,600 00†	+ 100 00
200 00	200 00	Shattuck Lecture	200 00	—
600 00	302 00	Cotting Luncheons	350 00	+ 250 00
10,250 00	8,195 00	General Administrative Expense (under supervision of President and Secretary)	9,100 00	+ 1,150 00
		<b>COMMITTEES ELECTED BY DISTRICT SOCIETIES</b>		
400 00	225 00	Executive	400 00	—
5,000 00	4,324 00	Legislation	5,000 00	—
600 00	456 00	Public Relations	600 00	—
		<b>STANDING COMMITTEES</b>		
200 00	Profit	Arrangements (Income or expense \$6,373 87)	400 00	—
50 00	40 00	Ethics and Discipline	50 00	—
35 00	10 00	Finance	25 00	—
100 00	18 00	Industrial Health	400 00†	+ 300 00
1,500 00	846 00	Medical Defense	1,500 00†	—
—	—	Medical Education	—	—
100 00	120 00	Membership	150 00	+ 50 00
7,000 00	2,012 00	Publications	200 00†	+ 6,800 00
70 00	214 00	Public Health	50 00	+ 150 00
7,500 00	7,397 00	Society Headquarters	4,100 00	+ 3,400 00

## DETAILED EXPENDITURES — 1947

## Expenses of Officers, etc.

*President*

Meals	\$33 39
Hotel Room	42 35
	<hr/> 75 74

Estimate for November-December	135 26
	<hr/> 211 00

*President-Elect*

Transportation January-May	74 00
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*Secretary*

Supplies	97 94
Printing and Engraving	1,515 31
Travel	270 92
Reporting meetings	168 50
Telephone	27 31
Mailing	141 76
Petty cash	117 10
	<hr/> 2,338 84

Estimate for November-December	900 00
	<hr/> \$3,238 84

*Treasurer*

Loomis and Sayles	1,218 72
Rent on box	18 00
Premium on bond	37 50
Hartshorn and Walter	315 00
Petty cash	12 17
Printing	271 95
Supplies	6 95
	<hr/> 1,880 29

Estimate for November-December	68 10
	<hr/> 1,948 39

*Director Medical Information and Education*

Estimate for November-December	110 32
	<hr/> 200 00
	<hr/> 310 32

*Delegates to A M A*

Shattuck Lecture	676 23
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Cutting Luncheons	450 00
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Deduct income Cutting Fund	148 00
	<hr/> 302 00

*General Administrative Expense*

Printing	498 55
Supplies	766 31
Clerical from Journal	90 00
Petty cash	237 91
Blue Cross premiums	119 25
Rental of typewriters	17 50
Telephone	488 23
Funeral flowers	35 00
Installation of machines	121 01
Inspection of machines	26 00
Rental of Sprague Hall	10 00
Dues	5 00
Stamps	68 25
Travel, Mr. Boyd	81 31
Travel to Chicago	151 16
Subscription to J A M A	8 00
Rental water cooler	25 35
	<hr/> 2,748 83

Estimate for November-December	194 00
Clerical work for year	5,252 00
	<hr/> 8,194 83

*Committees Elected by District Societies**Executive*

Meals	187 98
Petty cash	37 00
	<hr/> 224 98

Estimate for November-December	00 00
	<hr/> 224 98

*Legislation*

Supplies	27 50
Charles Dunn	3,500 00
Mimeographing	58 67
Travel	100 33
Dr. Bagnall to Washington	16 50
Reporting	116 23
Telephone	10 98
Meals	224 09
Petty cash	1 85
Subscriptions	200 00
	<hr/> 4,256 15

Estimate for November-December	68 10
	<hr/> 4,324 25

*Public Relations**Meals*

Estimate for November-December	155 56
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*Standing Committees*

	300 00
	<hr/> 455 56

*Arrangements**Income*

From booths	\$13 580 00
Tickets to party	144 00
Tickets to Annual Meeting	3,213 85
From Ladies' Committee	145 50
Statler overpayment	29 11
	<hr/> 17,112 86

*Expenses*

Golf prizes and Tournament	54 75
Printing	611 57
Telephone	27 52
Meals	374 50
Editing program	35 00
Stationery	73 65
Rental lanterns	147 00
Transportation, speakers	250 67
Badges	177 41
Statler	8,487 97
Erection booths	51 50
Music	55 00
Flowers	15 00
Sigors	85 00
Public relations	150 00
Petty cash	24 03
Buses	35 00
	<hr/> 10 656 97

*Estimate for November-December*

	81 00
	<hr/> 10 738 97

*Profit*

	6,373 99
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*Ethics and Discipline*

Meals	30 25
Legal opinion	20 00
Petty cash	20 00
	<hr/> 50 45

*Estimate for November-December*

	9 49
	<hr/> 59 95

*Less income from Brickley Fund*

	20 00
	<hr/> 39 95

*Finance*

Estimate for November-December	10 00
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*Industrial Health*

Meals	17 80
-------	-------

*Medical Defense*

Legal	846 08
Estimate for November-December	00 00
	<hr/> 846 08

*Medical Education**Membership*

Meals and Room	50 41
Clerical work, State House	25 00
Telegrams	6 89
Telephone	10 92
	<hr/> 93 22

*Estimate for November-December*

	26 81
	<hr/> 120 05

*Publications*

Directory, clerical	11 00
Estimate for November-December (Directory)	2 000 00
	<hr/> 2 012 00

*Public Health*

Massachusetts Central Health Council dues	10 00
Travel	109 70
Meals	37 01
	<hr/> 156 71

*Estimates for November-December*

	57 75
	<hr/> 214 46

*Society Headquarters*

Machines	34 675
Electricity	166 12
Cleaning	190 00
Rent	2,437 50
Office equipment	91 00
Carpentry and repairs	109 56
	<hr/> 6,471 36

*Estimate for November-December*

	925 37
	<hr/> 7,396 73

## Special Committees

*Bureau of Clinical Information*

Wages	1 800 00
Mimeographing	81 75
Telephone	79 95
Supplies	250 86
Stamps	35 00
Extra clerical	91 80
Petty cash	5 85

Estimate for November-December	2,569 21
	800 00
	3,369 21

*Fee Schedule*

Printing	31 39
Telephone	5 92
Travel	189 34

Estimate for November-December	224 65
	152 00
	356 65

*Malpractice Insurance Study*

Meals	19 08
Printing	33 35
Petty cash	3 15
Secretarial	110 00

Estimate for November-December	165 58
	165 58

*Medical Economics*

Meals	63 54
Estimate for November-December	00 00
	63 54

*N. E. Postgraduate Assembly*

Income	
Booths	1,005 00
Tickets	2,858 87
	5 863 87

Expenses	
Meals	18 09
Printing	396 64
Envelopes and addressing	437 44
Refund on rental space	15 00
Petty cash	1 35
Mailing	55 01
Mimeographing	53 50
Badges	85 56
Cash on hand for meeting	50 00

Estimate for November-December	1,094 39
	7 723 19
	4 817 78
Profit	1 016 09

*Postgraduate Education**Income*

Sale of tickets Sanders Theater	1 258 35
Payments from Commonwealth of Massachusetts	1 100 00
	2,358 35

*Expenses*

Printing	299 00
Meals and rooms	171 50
Typing	7 00
Mailing	13 93
Lectures and travel	5 027 16
Telephone	11 34
Lunches, Sanders Theater	1,335 30
Set-up Sanders Theater	406 43

Estimate for November-December	5 271 66
	00 00
	5 271 66

Less income	2,358 35
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Net expense	2 913 41
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*Postwar Loan Fund*

3% on 10 loans of \$500	150 00
Telephone	1 12

	151 12
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Estimate for November-December	30 00
	181 12

*Rehabilitation*

Meals	1 03
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*School Medical Services*

Meals	29 88
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*Special Services*

Post cards	60 00
Meals	301 8
	3 1 8

*Other Expenditures*

Refund to District Medical Societies	4 000 00
Dues, Council N. E. State Medical Society	100 00
To carry New England Journal of Medicine	5 000 00
Premium payment, pension plan (Mr. Boyd)	4 235 40
Taxes (social security and unemployment insurance)	507 55

## REPORT OF COMMITTEE ON FINANCE — BUDGET FOR 1948

BUDGET 1947	EXPENDITURES 1947		BUDGET 1948	CHANGE
\$4,000 00	\$4,000 00	<b>SALARIES</b>		
4,800 00	4 800 00	Secretary	Contingent*	—
2,500 00	2,500 00	Executive Secretary	4 600 00	—
—	3 750 00	Treasurer	2,500 00	—
		Director Medical Information and Education	8 000 00	+ 8 000 00
		<b>EXPENSES OF OFFICERS ETC.</b>		
300 00	211 00	President	300 00	—
300 00	74 00	President Elect	100 00	+ 400 00
1 500 00	3,239 00	Secretary	3 500 00	+ 2 000 00
2,000 00	1 948 00	Treasurer	2 000 00	—
—	110 00	Director Medical Information and Education	Contingent*	—
1 500 00	676 00	Delegates to A. M. A.	1 600 00†	+ 100 00
200 00	200 00	Shattuck Lecture	200 00	—
600 00	302 00	Cutting Luncheons	350 00	+ 250 00
10,250 00	8 195 00	General Administrative Expense (under supervision of President and Secretary)	9 100 00	+ 1 150 00
		<b>COMMITTEES ELECTED BY DISTRICT SOCIETIES</b>		
400 00	225 00	Executive	400 00	—
5,000 00	4,324 00	Legislation	5,000 00	—
600 00	456 00	Public Relations	600 00	—
		<b>STANDING COMMITTEES</b>		
200 00	Profit	Arra. Retreats (Income over expense \$6,373 89)	200 00	—
50 00	40 00	Ethics and Discipline	50 00	—
25 00	10 00	Finance	25 00	—
100 00	18 00	Industrial Health	400 00†	+ 300 00
1,500 00	816 00	Medical Defense	1,500 00	—
		Medical Education	—	—
100 00	120 00	Membership	150 00	+ 50 00
7,000 00	2,012 00	Publications	200 00†	+ 6,800 00
70 00	214 00	Public Health	750 00	+ 180 00
7 500 00	7 397 00	Society Headquarters	4,100 00	+ 3 400 00



## REPORT OF COMMITTEE ON FINANCE — BUDGET FOR 1948 (Concluded)

SPECIAL COMMITTEES				
3,750 00	3 369 00	Bureau of Clinical Information	3 500 00	— 250 00
365 00	357 00	Cancer	50 00	+ 50 00
200 00	166 00	Fee Schedule	50 00	— 315 00
75 00	64 00	Malpractice Insurance Study	200 00	—
1,000 00	—	Medical Economics	25 00	—
3,750 00	2 913 00	New England Postgraduate Assembly (Income over expenses \$1 016)	1 000 00	—
335 00	181 00	Postgraduate Education (Income \$2 358)	3 500 00	— 250 00
—	71 00	Postwar Loan Fund	—	— 335 00
—	30 00	Rehabilitation	—	—
—	361 00	School Medical Services	75 00	+ 75 00
		Special Services	300 00	+ 300 00
OTHER EXPENDITURES				
4 000 00	4 000 00	Refund to District Medical Societies	8 000 00	+ 4 000 00
100 00	100 00	Dues, Council New England State Medical Societies	00 00	—
\$	5 000 00	To carry <i>New England Journal of Medicine</i>	10 000 00	+ 10 000 00
—	4 233 80	Premium payment, pension plan (Mr. Boyd)	4 014 00	+ 4 014 00
—	507 58	Tax expense (Social security and unemployment insurance, newly required by Bureau of Internal Revenue)	670 00	+ 670 00
—	—	Contingent fund to cover (approximately) expenses of Director of Medical Information and Education, and possible change in salary of Secretary	9 500 00*	+ 5 500 00
\$64,070 00	\$67 220 38		\$86 359 00	+ \$22 789 00

\*Amount of Secretary's salary contingent upon possible change to full-time status budget of Director of Medical Information and Education contingent upon decision as to who is to be financially responsible for expenses of this office

†Anticipated expense of delegates to two A M A meetings carries over into 1948, as second meeting was not held until January 1948

‡Added expense due to request of A M A for delegates to Cleveland meeting in January, 1948

§The 1947 budget of the Publications Committee included \$2 000 for publication of directory and \$5 000 to carry *New England Journal of Medicine*. The Committee has requested authority to increase the latter figure to \$10,000

ESTIMATED INCOME	1947	1948	(not including \$5 000 allocation to Boston Medical Library)
Annual dues	\$54 450 00	\$108 900 00	
Non-resident dues	2 230 00	2 200 00	
Censors' fees	1,250 00	1 250 00	
General Fund income	5 200 00	5 200 00	
Committee on Arrangements	6 000 00	4 000 00	
Postgraduate Assembly	1 000 00	700 00	
Profit on sale of securities	770 00	600 00	
From <i>New England Journal of Medicine</i>	—	—	
	\$70 900 00	\$122,850 00	

## APPENDIX NO 6

## REPORT OF THE COMMITTEE ON CANCER

A meeting of the committee was held on November 28, 1947

The problem of cancer-detection clinics in general, and the proposed cancer-detection clinic at the Palmer Memorial Hospital in particular, were discussed. Critical analysis of the functions of a cancer-detection clinic as ordinarily set up shows that the objective of attempting to give the entire population periodic examinations to detect early cancer is impossible, both because of insufficient personnel (for example, it is estimated that it would take all the radiologists in the country a year to give the population a gastrointestinal x-ray series alone) and because of the tremendous cost (over one and a quarter billion dollars a year). Nonetheless, these clinics, largely fostered by lay organizations such as the American Cancer Society and the Donner Foundation, have become tremendously popular and some four hundred are in existence at the present time. At least forty states have clinics of this type.

The American Medical Association and the American College of Surgeons have recognized that there is much of value in these clinics and have laid down certain principles for their establishment and operation. In its recommendation made to the Council at the October meeting the Cancer Committee did not make clear certain important points in which the proposed cancer-detection clinic at the Palmer Memorial Hospital would differ from most of those already established.

This clinic is not planned simply as an addition to the four hundred already established in the country, in spite of the great popular demand for a clinic of this type. It is planned not merely to fulfill the function of finding early cancer in a limited number of patients or of assuring them that they have no sign of the disease. Rather, and far more important, it is aimed primarily at determining procedures of special value in detecting cancer that may be applied by the physician in private practice and at serving as a demonstration center for such procedures.

It is recognized that the best and most effective type of cancer detection should be the work done by the individual practitioner of medicine with his own patients. However, a great number of procedures that might be used in the doctor's office are perhaps not calculated to yield results commensurate with the time, expense and detail involved. The proposed cancer-detection clinic would serve as a proving ground for different types of diagnostic methods and as a center where doctors might come to determine procedures applicable to the problems of their own practice. A number of physicians have neither the time nor the equipment to give the type of examination they consider a person coming to them to determine the presence or absence of cancer should have, and a facility of this type to which they could refer such persons has definite value.

The work of the general practitioners would be augmented by the increased number of cases referred to him for management and treatment. It is desirable that patients accepted by the clinic should be referred by their physicians. In rare cases there may be persons who have no family physician and who might therefore be accepted for examination. In all cases, reference for treatment will be made to the physician of the patient's choice.

The relation of such a cancer-detection clinic to the already existing cancer clinics and tumor clinics throughout the Commonwealth has been carefully considered. Since the cancer and tumor clinics are planned for the patient who has a lesion, cancerous or noncancerous, and the cancer-detection clinic is for the person who considers himself well, there can be no conflict. Moreover, the cancer-detection clinic does not attempt therapy in any form.

The question has been raised whether such a clinic might not better be supported in part by voluntary gifts rather than by state or federal funds. This question is an entirely proper one, and it is believed that the support of such a clinic might better come from voluntary gifts if available, than from state or federal sources. In the present instance, however, public funds are at hand, and voluntary funds are not. If voluntary funds cannot be readily obtained, public funds should be accepted.

The committee believes that the Council was well advised in deferring action on its report at the October meeting. The intervening time has given opportunity for further study of the problem and for clarification of a number of aspects.

#### RECOMMENDATIONS

It is recommended that the report of the committee presented at the October meeting of the Council be taken from the table.

It is recommended that that and the present report of the Committee on Cancer be accepted by the Council.

It is recommended that the Council approve in principle the establishment of a cancer-detection clinic at the Palmer Memorial Hospital.

SHIELDS WARREN *Chairman*

#### APPENDIX NO. 7

##### REPORT OF THE COMMITTEE OF SEVEN

This committee was appointed to study the need for a full-time secretary and to define the duties of the Secretary, Director of Medical Information and Education and the Executive Secretary of the Society.

In recent years the growth of the Society has been rapid; its interests have broadened and the work of the Secretary's office has increased to so large an extent that the employment of a secretary who devotes his entire time to the work of the Society is urgently needed. The committee recommends that a secretary who devotes his entire time to the work of the Society be henceforward employed.

In defining the duties of the Secretary, the Director of Medical Information and Education, and the Executive Secretary of the Society, the committee believes that certain changes in the By Laws are necessary, therefore the following changes in the By Laws are recommended.

#### BY LAWS

##### CHAPTER IV

##### *Appointment of Director of Medical Information and Education*

**Section 8.** The Council may appoint and dismiss a Director of Medical Information and Education.

##### *Salaries and Appropriations*

**Section 9.** The Council shall vote the salaries of its officers and employees; shall determine the tenure they may respectively have in their offices; the appropriations for its officers, employees and committees; and such other appropriations as it deems suitable.

No officer, employee, or committee shall exceed the voted appropriation.

No salary to any officer or employee and no regular appropriation shall be increased except on recommendation of the Committee on Finance and by vote of the Council.

The Treasurer is authorized on recommendation of the Committee on Finance to pay such monies as may be necessary in the event of emergency, the existence of which shall be determined by the President.

#### CHAPTER VI OFFICERS

##### *Duties of Secretary*

**Section 4.** The Secretary shall attend all meetings of the Society, the Council and the Executive Committee, and shall record their respective proceedings in separate volumes.

He shall cause to be engrossed and shall sign the diplomas of new fellows if satisfied that they have met the requirements of Chapter I and shall issue all diplomas and certificates of fellowship.

He shall notify fellows of votes by the Council or Executive Committee granting permission to retire, to resign, to transfer district membership or to have dues remitted, and of votes depriving them of or reinstating them in the privileges of fellowship.

He shall be *ex-officio* secretary of all boards of trial the Board of Supervising Censors, the Committee on Publications, the Committee on Ethics and Discipline, and the Committee on Membership, and shall keep the records of each in separate volumes. He shall be a member *ex-officio* of all other committees without power of vote.

He shall notify members of committees of their appointment and of the duties assigned them. On advice of their chairman or secretary he shall give due notice of the time and place of their several meetings.

He shall have custody of the seal of the Society and of all books, papers, manuscripts, prints and paintings belonging to the Society, except such as are in charge of the Treasurer.

He shall issue notices of the meetings of the Council according to such rules as the Council may adopt. He shall issue to every fellow one month before the annual meeting of the Society a program listing the time and place of that meeting and of the stated meetings of the Council, the boards of censors for that year and information concerning the payment of assessments and the distribution of publications if there are any proposed amendments of the By Laws, he shall provide that each program is accompanied by a copy thereof.

He shall transfer fellows from one district to another under the terms of Chapter III, Section 3 and shall report to the Society at its annual meeting the changes in membership during the year.

He shall conduct official correspondence and shall notify officers and delegates of their appointments and of their duties.

He shall keep a directory of the fellows and shall publish the same under the direction of the Committee on Publications at such intervals as may be determined by the Council. He shall furnish this on request to fellows not in arrears.

He shall have jurisdiction over the work of the Executive Secretary and over the work of the Director of Medical Information and Education.

##### *Duties of Executive Secretary*

**Section 7.** The Executive Secretary under the jurisdiction of the Secretary shall assist the officers, the Council and such committees as may request his services. He shall also serve as manager of the general office and shall help in the arrangement of the annual meeting and of such other meetings as are sponsored in whole or in part by the Society.

##### *Duties of Director of Medical Information and Education*

**Section 8.** The Director of Medical Information and Education under the jurisdiction of the Secretary shall promote in an ethical manner the educational usefulness of the Society to the fellows, to all licensed physicians in Massachusetts and to the public. He shall also assist the officers, the Council and such district societies or committees as may request his services.

##### *Expenses of Officers, Executive Secretary,*

##### *Director of Medical Information and Education, and Committees*

**Section 9.** The traveling and incidental expenses of the officers of the Executive Secretary, of the Director of Medical Information and Education, of the committees of the Society elected by districts and of standing committees of the Society on request, shall be paid by the Treasurer on presentation of an itemized bill duly approved by the President.

REGINALD FITZ, Suffolk *Chairman*  
FRANK B. CARR, Worcester  
WILLIAM A. R. CHAPIN, Hampden  
LAWRENCE R. DAME, Franklin  
PERCIE H. LEAVITT, Plymouth  
Dwight O'Hara, Middlesex South  
WALTER G. PHIPPS, Essex South  
EDWARD P. BAGG, *ex-officio*  
DANIEL B. REARDON, *ex-officio*

#### APPENDIX NO. 8

December 12, 1947

Hamphrey L. McCarthy, M.D.  
Chairman, Massachusetts Medical Society  
479 Beacon Street  
Boston, Massachusetts

Dear Dr. McCarthy:

The following is a report of fee basis operations during the year 1947.

A new treatment procedure and form was evolved, after many months of discussion between Boston Regional Office Veterans Administration officials and officials of the Mass

sachusetts Medical Society. The prime object was to devise some system that would simplify the many exacting requirements of Government paper work detail and reduce bookkeeping for private doctors to a bare minimum.

The resultant procedure was inaugurated on July 1, 1947, and aside from several minor operational problems, did not present any unusual difficulty.

At the time of installation of the procedure, the Veterans Administration had a processing backlog of doctors' bills for medical treatment, amounting to almost seven months' work. Since the introduction of the new procedure this backlog has been virtually eliminated. At the present time the Boston Regional Office is within thirty days of being current on the payment of most bills for medical treatment.

Two major difficulties were experienced by the Veterans Administration in paying for medical treatment under the new system, the first being that a large percentage of doctors did not submit their bills within fifteen days from the end of the month in which treatment was rendered. It should be noted that bills submitted on or before that date will be paid promptly. Bills received after that date may be delayed as long as two or three months in payment. It therefore behooves every doctor to forward these forms without delay.

The second major difficulty is the incorrect preparation of the statement of services rendered.

The following are a few of the errors for which it was necessary to return the bills for correction:

1. Signature and registration number missing from lower right hand corner of Report of Treatment.
2. Signature and address missing from Statement of Services Rendered.
3. Report of Treatment is incomplete.
4. Dates and fees shown on Statement of Services Rendered does not register through cards onto pink copies. If pen is used, the entries should be made on both copies. If indelible pencil is used, entries will register through carbon satisfactorily.
5. Entries must be made in ink, by typewriter or indelible pencil. Ordinary pencil writing cannot be accepted.
6. Doctor's address is missing.
7. Statement of Services Rendered is incomplete.
8. Totals not shown on Statement of Services Rendered.
9. Fee charged on Statement of Services is in excess of fee authorized.
10. The number of visits charged on the statement is in excess of the number of visits authorized.
11. Treatments shown on Report of Treatment is not the disability for which authorization is granted.

During the month of July it was necessary to return for correction approximately 50 per cent of the bills rendered. This percentage has steadily declined until a level of approximately 7 per cent has been maintained for two months.

As a result of the many suggestions received from officials of the Massachusetts Medical Society and physician members, the Treatment Authorization Form was revised slightly

on the first of December and will also be used to authorize examinations for compensation purposes.

On the first of December also the list of general medical physicians, which formerly accompanied the authorization, was eliminated. Instead a letter is attached, instructing the veteran to report to any physician who has been approved for the care and treatment of veterans by the Massachusetts Medical Society and the Veterans Administration.

Veterans requiring specialistic treatment will be furnished with a list of qualified specialists.

At the present time there is a backlog in the payment of bills for examinations, amounting to about three months' work. It is anticipated that by the use of Form 10-900 this backlog will be eliminated in the near future.

During 1947, 28,228 examinations were made by fee-basis physicians at a total cost of \$227,793. During the same period 117,788 treatments were given at a cost of \$447,234.

The percentage break-down by types of examination and treatment is shown below:

TYPE	EXAMINATION TREATMENT	
	%	%
Ear, nose and throat	3	3
Eye	1	1
Genitourinary and gynecologic	2	1½
Heart	1½	1
Neurologic	1½	1½
Orthopedic	5	3
Physical therapy	—	8½
Psychiatric	8	5
Dermatology	1½	5½
Tuberculosis	—	1½
Venereal	—	—
General surgical	1½	1½
General physical	9½	60
X-ray and electrocardiographic	52½	1½
Laboratory	14	—
All other	2	3½

On the first of November a new fee schedule became effective as a result of an agreement between the Massachusetts Medical Society and the Veterans Administration. Certain fees may not be entirely adequate, however, the Medical Society is presently negotiating for increases where indicated.

A board of review has been established by the Massachusetts Medical Society to which private physicians and the Veterans Administration may present their problems regarding veterans' care and which already has handled and adjudicated many cases satisfactorily.

On the whole the year has been marked by better relations between private physicians and the Veterans Administration. Most physicians have been very patient and understanding, regarding the problems confronting the Veterans Administration during a year of tremendous expansion, and their practical suggestions, freely given, have contributed to a great extent to the evolution of a sounder and more efficient veterans' care program.

Officials of the Massachusetts Medical Society deserve much credit for many hours of devoted work, in solving problems of policy and procedure and in liaison with the Veterans Administration.

STEPHEN J. DALTON, M.D., Chief Medical Officer

Regional Office  
Veterans Administration  
Boston, Massachusetts

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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## CASE 34151

### PRESENTATION OF CASE

A fifty-nine-year-old woman entered the hospital because of hemoptysis.

Two months before admission she had an attack of "grippe," and one week later coughed up a large clot of blood. One month before admission she coughed up another blood clot and had occasional streaks of blood in the sputum. She lost 5 pounds in the two months prior to entry.

Four years before entry a left nephrectomy had been performed at another hospital, and a hypernephroma removed, following which she received twenty courses of x-ray treatments to the left nephrectomy scar. One and a half years later she entered this hospital with a soft mass in the left lumbar region extending from the iliac crest. X-ray examination at that time revealed a defect, 4 by 6 cm., in the crest of the ilium. The upper fourth of the left ilium was resected. Pathological examination revealed metastatic renal-cell carcinoma. Two years before entry diabetes was discovered, and she had taken 35 units of protamine-zinc insulin daily, augmented by 5 to 6 units of regular insulin.

Physical examination revealed a well developed and well nourished woman. A Grade III apical and aortic systolic murmur, which had been recorded on the previous admission, was heard. Diminished breath sounds and increased tactile fremitus were found over the left lower lobe. There was a large incisional hernia in the scar in the left flank.

The temperature was 99°F, the pulse 78, and the respirations 18. The blood pressure was 135 systolic, 65 diastolic.

Examination of the blood disclosed a hemoglobin of 10.3 gm and a white-cell count of 7500, with 56 per cent neutrophils, 30 per cent lymphocytes, 4 per cent eosinophils and 1 per cent basophils. Urinalysis showed a specific gravity of 1.012 and was negative for albumin, sugar and diacetic acid. The fasting blood sugar was 236 mg., the total protein 7.4 gm., and the nonprotein nitrogen 24 mg. per 100 cc. The prothrombin time was 21 seconds

(control, 16 seconds). A blood Hinton test was negative. A sputum smear was negative for tumor cells.

X-ray films of the chest showed an elevated diaphragm on the left side, with a hazy density involving most of the left side of the chest (Fig. 1). On the lateral view there was a band of increased density 3 cm. in diameter along the anterior portion of the chest wall, suggesting partial collapse of the left upper lobe. The right lung field was clear.



FIGURE 1

except for some areas of atelectasis just above the diaphragm. The heart was not unusual.

On the third hospital day a bronchoscopy was performed.

### DIFFERENTIAL DIAGNOSIS

DR. ALLEN G. BRAILEY: This patient had several things the matter with her, any one of which might have caused death under suitable circumstances. In fact we are very generously provided with three diagnoses concerning which there seems little ground for argument: she had diabetes mellitus, she probably had aortic stenosis, whether rheumatic or not is not clear, and she had renal-cell carcinoma. But she also had something else, the nature of which is not nearly so obvious—something that involved the lung or bronchus and was signalized by gross hemoptysis and by various abnormal physical and x-ray signs.

MAY we see the x-ray films?

DR. STANLEY M. WYMAN: This film which was taken three years before the present admission, shows the heart to have a prominent left ventricle, consistent with hypertension or aortic stenosis. The

lung fields are clear. This is a film of the lesion of the left iliac bone described, taken at the same time as that of the chest. This is the postoperative film taken later. The two films describing the lesion in the chest show the left leaf of the diaphragm to be elevated. There is a poorly defined area of hazy density overlying the upper two thirds of the left lung field medially, leaving a clear peripheral zone. The heart shadow shows a prominent left ventricle, but is otherwise not remarkable. The right lung field is clear. There is atelectasis at the base. The zone of density described in the anterior portion

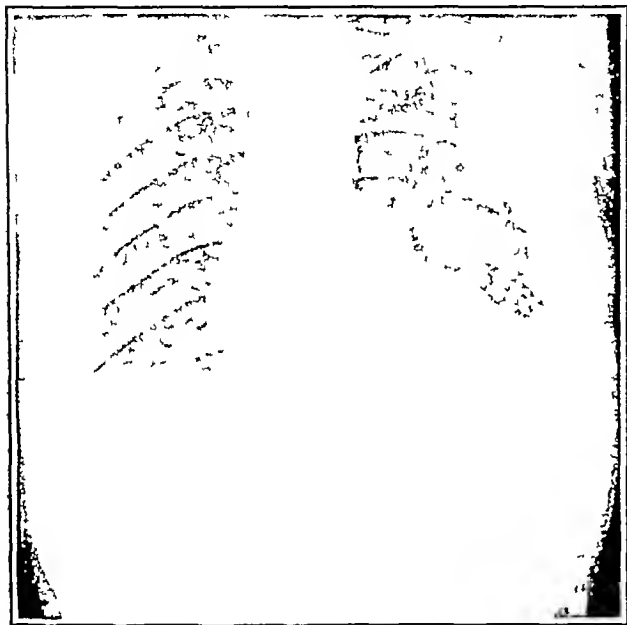


FIGURE 2

of the chest in the lateral view is seen as a band of indefinite character. In this view it is quite consistent with partial collapse of the left upper lobe.

DR BRAILEY: Can you see the bronchus to the left upper lobe?

DR WYMAN: No, not adequately. There are no bony defects and no evidence of masses in the mediastinum or hili.

DR BRAILEY: The significant features of the chest lesion appear to be that it produced collapse of the left upper lobe and resulted in hemoptysis. It does not seem likely that any very extended differential diagnosis will be necessary, for there are not many conditions that will produce these changes. In fact, I think that only tuberculosis and neoplasm deserve serious consideration. Endobronchial tuberculosis leads inevitably, in time, to bronchial stenosis. It can also ulcerate and result in hemoptysis, but very rarely massive hemoptysis. But how massive was the hemoptysis? The record states that the patient coughed up "a large clot" of blood. But a large clot is more suggestive of a long period of

gentle oozing than the sudden rupture of a sizable vessel. I am therefore not sure that the bleeding was ever more than very moderate. On the other hand, I do not believe we can exclude the possibility of a small parenchymal cavitation near the hilus or behind the heart, which might have provided any degree of bleeding. It should be noted in passing that she was diabetic and that diabetic patients are especially prone to tuberculosis. A single sputum specimen is said to have shown no tumor cells. We are not told whether tubercle bacilli were looked for in the sputum or gastric contents. I am sure that a search of the sputum at least was made, and we must conclude therefore that no bacilli were found. Is it proper to ask how much of a search for tuberculosis was made?

DR TRACY B. MALLORY: Judging from the record, I should say that the search was not extensive.

DR BRAILEY: Let us leave tuberculosis for the moment and consider neoplasm. An adenoma of the bronchus might easily produce these symptoms and signs. It is a lesion that is prone to bleed and may bleed very briskly. It, of course, readily occludes the bronchus. In fact, the sequelae of such occlusion often bring the patient to the doctor. To be sure, adenoma is likely to appear at an earlier age, but no age is exempt. If we regard this history as indicative of a good deal of bleeding, then we have an argument in favor of adenoma as opposed to cancer, for bronchiogenic cancer, at least, is apt to result in blood streaking but not massive hemoptysis. The state of relative good health is perhaps a straw in favor of a benign lesion. Incidentally, one wonders if the "grippe" that is said to have ushered in the present illness was a transient pyogenic infection of the collapsed lobe.

Did the patient have bronchiogenic cancer? I think so, but it is a little unusual for a woman in previously good health to present gross hemoptysis as the first sign of cancer of the bronchus. However, bronchiogenic cancer remains a very definite possibility. There is the difficulty that if we agree that she had bronchiogenic cancer we give her not three, but four, potentially fatal diseases, and two of them are unrelated carcinomas. Multiple primary malignant tumors are not very rare. Drooker<sup>1</sup> has reported the history of a man who was successfully operated upon in this hospital for three separate unrelated cancers. Warren<sup>2</sup> reported in 1944 that in 3907 autopsies on patients with cancer, 6 per cent had two or more unrelated cancers. He and his colleagues estimated that the chance of developing cancer *de novo* is about eleven times greater in the person who already has a malignant tumor.

Finally, we must explore the possibility that the chest lesion was a metastasis of the renal-cell carcinoma. I see no reason why tumor cells might not lodge in the bronchial wall or so close to the bronchus as to erode or grow into the bronchus, with occlusion of the tube and subsequent ulceration.

tion and bleeding. The very fact that this case is presented for discussion makes me wonder if that is not precisely what took place, but such a pretty series of events must be excessively rare and to make such a diagnosis would require an unreasonable love for long shots.

I do not know how to decide between these various possibilities. Clinically, no such decision should have been made. The decision should merely have been to bronchoscope, but since I am expected to make a guess, I think it better judgment to guess that the patient had an adenoma of the bronchus.

DR ERNEST M. DALAND: I saw this woman on the first entry, when she had a metastatic lesion in the ilium and, at that time, no other metastases. We removed the crest of the ilium. There was quite a sizable tumor growing out through it. She did very well so far as that was concerned, at the time, except that she developed a large hernia in the scar. I subsequently followed her, and she came to me when she had the hemoptysis.

#### CLINICAL DIAGNOSIS

Primary bronchogenic carcinoma

DR BRAILEY'S DIAGNOSES

Renal-cell carcinoma  
Diabetes mellitus  
Rheumatic heart disease  
Adenoma of bronchus

#### ANATOMICAL DIAGNOSIS

Endobronchial metastasis of renal cell adenocarcinoma

#### PATHOLOGICAL DISCUSSION

DR EDWARD B. BENEDICT: Bronchoscopy showed a slightly irregular mass completely obstructing the left upper lobe bronchus. A portion of it looked vascular, — that is, it was a dark, hemorrhagic color, — and I hesitated to take a biopsy for fear of serious hemorrhage. But I did take hold of it with the forceps, and instead of my obtaining a biopsy specimen, the whole tumor mass came out. It was the size of the end of a finger. There was no bleeding. After removing it, I looked in through the bronchoscope, using the right-angle telescope, and could see all the terminal orifices of the upper lobe, and there was no sign of tumor in the bronchus.

DR MALLORY: The tumor that Dr. Benedict so successfully removed showed an adenocarcinoma of clear, vacuolated cells, characteristic of renal-cell adenocarcinoma, and without doubt a metastasis from the original hypernephroma. I believe that the patient has been bronchoscoped once again.

DR BENEDICT: About a month after the original bronchoscopy we looked in again and there was no sign of anything in the bronchus.

DR MALLORY: There was considerable debate regarding whether or not this patient should have further surgery.

DR BENEDICT: Dr. Daland and I talked that over. Since she has had two metastases she must have disease elsewhere, and we did not want to put her through another operation with the diabetes and so on. She also has developed an abdominal mass, which Dr. Wyman will demonstrate.

DR WYMAN: These two films show very nice aeration of the left upper lobe with a small amount of fluid in the costophrenic sinus (Fig. 2). Now there is a huge mass in the left midportion of the abdomen, which in one film seems to lie far posterior and displaces the stomach. It is consistent with a large recurrent tumor mass in the region of the left kidney.

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- Warren, S., and Ehrenreich, T. Multiple primary malignant tumors and susceptibility to cancer. *Cancer Research* 4:554-570, 1944.

#### CASE 34152

##### PRESENTATION OF CASE

**First admission.** A fifty-nine-year-old business executive entered the hospital complaining of chest pain.

A year and a half before admission the patient, who had been otherwise asymptomatic, developed mild anginal pain, followed in a few weeks by severe pain diagnosed as coronary thrombosis. Serial electrocardiograms were said to have shown a posterior myocardial infarct and then gradually to have returned to normal, the patient returned to his work and moderate activity. Seven weeks before admission he developed a bad cold, with a dry cough and slight fever, but no chest pain, he continued to cough and felt vaguely not well. Examination revealed no sign of disease. He did note, however, midepigastria distress, and one week later discomfort in the right side of the chest, extending from the xiphoid process to the right midaxillary line. This discomfort was described as dull in character but did prevent sleep, it was improved by lying on the left side and aggravated only slightly on deep breathing. There was no hemoptysis, dyspnea or orthopnea. Two weeks later he was noted to have a friction rub in the right lower portion of the chest and therefore was put to bed. The pain became worse and spread to the left side of the chest.

Physical examination was remarkable only in showing localized tenderness over both lung bases posteriorly, with fine moist rales. The legs were normal. There was no evidence of thrombosis. A chest film showed numerous areas of increased density in both lower-lung fields, lying close to the

pleural surfaces and varying in shape from round to linear. There was a small amount of fluid in both pleural cavities. The patient was treated for ten days with a course of dicumarol and discharged after improvement of the pain on 200 mg of dicumarol every three days. Despite this fairly large dosage of dicumarol the prothrombin time never went above 25 seconds.

*Final admission* (two weeks later) The patient was readmitted because of persistence of the dull aching pain in the right side of the chest. The pain was aggravated by breathing and lying down but still with little cough and no hemoptysis. An additional history, first elicited at this time, revealed intermittent episodes of epigastric distress and "indigestion" for three months, occurring between meals and at night but unrelated to food intake.

Physical examination showed a man who appeared ill, had lost weight and was in considerable discomfort, with pain in the right side of the chest and indigestion. There was a firm, nontender, round lymph node, 1.5 cm in diameter, in the left inguinal area. Both lung bases were dull, with moist rales and diminished breath sounds. The liver edge was palpable 2 cm below the costal margin, but not tender, the left lobe was palpable and questionably irregular.

Urinalysis showed only a + test for albumin and rare granular and hyaline casts in the sediment. The prothrombin time was 21 seconds (control, 16 seconds). The white-cell count was 8300. The photohemoglobin was 14.6 gm per 100 cc.

X-ray films of the chest disclosed no change. Barium given by mouth showed no abnormality in the stomach or duodenum. The cephalin-flocculation test was normal. The total protein was 6.9 gm per 100 cc. A determination of the acid phosphatase was 1.7 units per 100 cc, the phosphorus 3.8 mg, and the alkaline phosphatase 19.2 units per 100 cc.

The patient failed fairly rapidly. He continued to have pain in the right side of the chest and back and died three weeks later.

#### DIFFERENTIAL DIAGNOSIS

DR MERRILL SOSMAN\* This patient gave a characteristic clinical history of pulmonary infarcts. The x-ray films suggest pulmonary infarcts. He was treated for pulmonary infarction, so that it is obvious that there must be a trap here some place. The things that are missing are hemoptysis and an acute sudden episode, such as that generally occurring with pulmonary infarction. There was no tenderness in the calves, that fact was stressed. The pain in the right side of the chest continued, and the patient died three weeks after the second admission. I do not know whether or not a biopsy of a lymph node was done.

What else could have produced this history and x-ray findings, which so strongly suggest pulmonary

infarction? The first thing to think of is tumor emboli or tumor infarcts from some concealed source. The source is usually the abdomen and often retroperitoneal. We must therefore think about malignant lymphoma as a possible source of these pulmonary manifestations. There was no anemia to go with a primary lesion of the gastrointestinal tract, and the gastrointestinal examination was apparently negative, although there was one small questionable area. What else could have produced such a case? A pancreatic tumor will give a history and findings of this type. Carcinoma of the pancreas, occasionally renal carcinoma and occasionally rare tumors of the genital ridge, very rapidly growing and malignant, kill a man this quickly, with metastases that appear like infarcts in the lung.

The second group of possible causes to be considered are the rare infections. The infection, such as is presumed to produce periarteritis nodosa, is really an allergic phenomenon, I think. This patient had a cold and then got worse. I am rather inclined to lean on the syndrome of periarteritis nodosa as being more logical than metastatic tumor. The monograph written by Armstrong, Bailey and Sosman, but never published, states that periarteritis nodosa is a febrile disease, and this man had a little fever. The local presenting symptomatology depends entirely on the localization of the arterial involvement. Any organ or system may be involved. The ones involved most commonly are the kidneys, — 75 per cent of all patients with periarteritis nodosa had definite renal involvement, — and when that occurs the outlook is unfavorable. This patient had albumin and casts but no blood in the urine. I would have expected to see red cells or hematuria. The heart is involved in 60 per cent of cases. I do not know whether or not this patient had definite coronary-artery disease a year and a half previously. Clinically, the evidence of heart involvement is much less frequent, very often it is a surprising finding at autopsy. The gastrointestinal tract is involved in one third of the cases, producing the most widespread and variable symptomatology of all. The symptoms may be very mild, consisting of a discomfort such as this man had, or they may be very acute and simulate an acute surgical condition of the abdomen. In fact, some patients operated on for acute perforation or strangulation have been found to have periarteritis nodosa in a segment of the bowel. The liver is involved in periarteritis nodosa — I cannot find the exact percentage of cases. We notice that the phosphatase in the case under discussion was 19.2 units per 100 cc. With nothing demonstrable in any of the bones it makes me think that the elevated phosphatase was due to marked liver involvement. The lungs are involved in periarteritis nodosa much more commonly than one might think, the condition may simulate a

\*Radiologist Peter Bent Brigham Hospital, Boston

miliary tuberculosis and, at times, unresolved pneumonia or infarct. There probably are actual infarcts in some areas of the lung. That would fit in here very well. The eosinophilia that is stressed so often in reports of periarteritis nodosa apparently occurs only if the patient had preceding asthma. That limits the group to the 10 per cent of patients who do get eosinophilia. However, it does not rule it out. We have no differential blood smear. I assume that it was normal. There was no eosinophilia but no history of asthma, so that we would not expect it. There was no obvious inflammation or tenderness or muscle pain in the extremities. The subcutaneous tender nodules, which on biopsy are apt to give a characteristic lesion, are missing here. The leukocytosis that usually occurs in periarteritis nodosa is missing. The globulin is very often increased. The total protein may not be increased, but there may be an inversion of the albumin-globulin ratio, which is not mentioned in the record — the determination probably was not done.

There is no history of any previous injection of serum or any administration of sulfonamides. It would be interesting to know whether sulfonamides were given during the first chronic attack or the febrile attack. Sensitivity to any agent apparently precipitates the full blown disease.

Going over the x-ray films several times, we see a rather steadily progressive involvement of the bases of both lungs. Those who have seen the films or are close enough can find little triangular nodules well out in the periphery of the lung, mostly in the bases. Fluid developed on the right side and, toward the end, on the left side. All the films show one dense area, which is probably in the anteromedial section of the right lower lobe, possibly in the inferior section of the middle lobe, which looks like atelectasis. That raises the question of primary bronchiogenic carcinoma with rapid spread. The history is so short and the downhill course so rapid that it does not fit a case of primary carcinoma of the lung, which must be considered, however.

The gastrointestinal films are said to have been normal. The man who does the fluoroscopy has a great advantage over anyone looking at the films. He can detect individual lesions and get detailed spot films. The fact that they were not taken means to me that he did not see anything suspicious. There is an area about the middle third of the lesser curvature that looks irregular on the film six hours after the administration of barium, a calcified area or a small barium residue high up on the left flank. That may be of significance and may indicate a "carcinoma occulta" of the stomach, often very small, no bigger than the thumbnail. It may metastasize widely through the lungs and liver, but one may be unable to pick up the original lesion

in the x-ray film. In fact Dr Wolbach admits that he has difficulty at times in finding the primary tumor in the stomach.

To sum up the evidence, the three possibilities that occur to me are a rapidly growing malignant tumor, probably in the abdomen and most apt to be retroperitoneal, such as, pancreas, kidney, or retroperitoneal lymphoma, bronchiogenic carcinoma, possibly primary in the right lower lobe, and the very remote possibility of carcinoma occulta of the lesser curvature of the stomach. The other possibility is the one I have taken more time on — that is periarteritis nodosa. I have looked up the alkaline phosphatase in Greenstein's *Biochemistry of Cancer* and find that the alkaline phosphatase is given in nearly all conditions except periarteritis nodosa. I was not able to find out whether periarteritis nodosa raises the phosphatase. However we can rule out bone diseases from the x-ray film and blame the increased alkaline phosphatase on marked liver damage.

DR TRACY B. MALLORY: Are there any other comments or any alternative diagnoses?

DR SOSMAN: I would like to have some of these men help lead me on to the correct track. Dr Bauer, what have you got to say?

DR WALTER BAUER: I am surprised that you gave such a long dissertation on periarteritis nodosa in this case. I am much more inclined to believe that the patient had a retroperitoneal neoplasm, with metastases, or even carcinoma of the stomach seems to be a more likely possibility.

DR SOSMAN: Would it kill the patient that quickly? I would expect a more prolonged course.

DR BAUER: He had had myocardial infarction. Nothing is said about the manner of death.

DR MALLORY: There was no evidence of congestive failure.

DR BAUER: We certainly see eosinophilia in periarteritis nodosa in the absence of asthma. In our series about one third of the patients have eosinophilia, and that varies from time to time, being present on one occasion and absent on another. I never thought of the eosinophilia of periarteritis nodosa as occurring in people with asthma as a manifestation of disease. Certainly, that has not been borne out in our experience.

DR SOSMAN: You see a great many asthmatic patients here. Dr Rackemann has a large clinic.

DR MALLORY: Dr Robbins, do you agree with Dr Sosman?

DR LAURENCE L. ROBBINS: Dr Sosman has covered the things that we considered in our differential diagnosis, and I have to admit that early in the x-ray examination we were quite content that these were multiple pulmonary infarcts in the healing stage. The first film was taken approximately seven weeks after the original acute episode, and we thought they were consistent.



## CLINICAL DIAGNOSIS

## Carcinomatosis

## DR SOSMAN'S DIAGNOSIS

Periarteritis nodosa?

Pulmonary metastases (tumor emboli) from retroperitoneal tumor?

## ANATOMICAL DIAGNOSES

*Carcinoma of tail of pancreas, with invasion of spleen, left adrenal gland and posterior wall of stomach and metastases to liver and lungs*

Coronary sclerosis, with occlusion

Infarct of heart, old

Hydrothorax, bilateral

## PATHOLOGICAL DISCUSSION

DR MALLORY Shortly before death a lymph node from the groin was removed for biopsy and found to contain metastatic carcinoma, too undifferentiated to permit any guess regarding the primary site of the tumor. At autopsy many metastatic foci were found in the lungs and liver but no infarcts of the lung. There was a small ulcer on the posterior wall of the stomach. Behind this, in the tail of the pancreas, was a mass of tumor, which had directly invaded the spleen, the lower surface of the diaphragm and the left adrenal gland. It was our impression that the tumor was primary in the pancreas, with secondary involvement of the stomach rather than vice versa. We found no metastases to the skeleton. The autopsy also showed the scar of the old infarct of the heart in the posterior part of the interventricular septum,

and occlusion of the descending branch of the left coronary artery.

DR ALFRED KRANES How extensive were the metastases to the liver?

DR MALLORY They were numerous but small, replacing perhaps a third of the liver substance.

DR KRANES It hardly seems enough to warrant such a rise in phosphatase.

DR MALLORY No, jaundice never developed.

DR ROBBINS Was it your impression that the pulmonary metastases were arterial emboli?

DR MALLORY I think they probably were.

DR SOSMAN You would explain the shadows in the lung as vascular metastases?

DR MALLORY All metastatic nodules.

DR SOSMAN One thing I called attention to was the area in the left upper quadrant in the region of the tail of the pancreas, unfortunately about the same region as the irregularity in the stomach. I said that it looked more like calcification than residue of barium. Carcinoma of the pancreas not infrequently contains areas of calcification. I found that out the hard way. One of my students saw some calcified areas in the liver and I asked him what they were. He said, "metastases." I said, "You can throw that out because metastases never calcify, with the exception of primary osteogenic sarcoma of bone." The patient was later explored and found to have carcinoma of the pancreas with calcification in the original tumor and also calcification in the liver metastases, so that my absolute "no" was wrong again. It is quite possible that this shadow represented calcification in a primary tumor of the pancreas.

DR MALLORY I cannot answer that because we did not look for it.

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## THE NATIONAL HEALTH PROGRAM

THE hearings before the Senate Subcommittee on Health on the Taft Bill (S-545) and the Wagner-Murray-Dingell Bill (S-2143), which began on May 21, 1947, will probably terminate shortly. In the three volumes of evidence already published and available there is much valuable information and some misinformation.

Out of the confusing and conflicting testimony grows a belief that there will not be any report favoring a compulsory program for sickness insurance from this committee or this Congress. It is also improbable that the Taft Bill as such will be reported out of committee. Legislation involving

huge expenditures would have to present convincingly good remedies for a demonstrably bad situation to get favorable consideration at this time.

It appears that as more people know more of the fundamentals, there is less support for the Social Security Board's plan. Chairman Smith circularized the governors of all the states and found that none favored the Wagner-Murray-Dingell Bill, whereas twenty-five favored the Taft Bill in principle. Even Governor Warren of California, who fought hard for a plan in his own state, is opposed to the Wagner-Murray-Dingell Bill and to socialized medicine.

In time evolutionary steps will probably be taken providing federal grants-in-aid to states where there is recognized inability to meet existing needs. The Government has so pre-empted tax sources that some states not in the needy group find federal subsidy acceptable.

The bill recently filed by Senator Saltonstall providing grants for local health units and another for school health services (S-1290) need clarification of purpose on such items as treatment. Steps leading toward the inclusion of a medical-care program in any legislation should be taken with extreme caution. At the hearing on this bill Dr. Martha Eliot, associate chief of the Children's Bureau, advocated thorough medical examination of school children every three or four years in preference to superficial annual inspections. Authorities on school health programs have been trying to persuade the Massachusetts legislature to adopt this point of view.

When tax dollars are sent to Washington for grants-in-aid programs it must be realized that states like Massachusetts are paying more than they receive in return. So far as the difference goes to needy states, we should not complain, but we should be realistic in weighing values received on federal programs. The Government has nothing to give that it has not first taken away.

The new Social Security administrator, Oscar Ewing, is calling a group to a conference early in May to formulate a ten years' program for health. This can be a valuable event for the nation, but it must be remembered that the board may have pre-packaged programs that need critical study, however well conceived they seem.

## GREATER BOSTON COMMUNITY SURVEY

OPERATING costs of social and health agencies in the Boston area, paralleling the cost of living in general, have scaled new heights. Deficits are accumulating, and the Greater Boston Community Fund, the Dutch uncle of them all, is feeling the pinch. Established in 1935 to raise funds for 115 agencies in municipal Boston, this super-agency must now provide the sinews of peace for 339 agencies serving fifty-five contiguous communities.

The writing on the wall has become more apparent. As a result of the present disturbing condition the governing boards of the Greater Boston Community Fund and the Greater Boston Community Council early last year invited Robert Cutler, president of the Old Colony Trust Company, to head a committee of citizens to direct a Greater Boston Community Survey of Social and Health Needs and Services.

Mr. Cutler, with no apparent difficulty, persuaded one hundred and eighty out of a panel of one hundred and eighty-four leading citizens to serve on such a committee. In March, 1947, an executive committee of sixteen members was appointed. The field to be covered in the survey has been divided into five divisions, comprising public health, hospitals, recreation and group work, voluntary case-work and statistics and public welfare. The director of the survey is Robert P. Lane, for twelve years executive director of the Welfare Council of New York City. The section on public health is under the direction of Ira V. Hiscock, Sc.D., chairman of the Department of Public Health of Yale University, assisted by Dr. Hugh R. Leavell, professor of public-health practice of the Harvard University School of Public Health, and an advisory group, that on hospitals is under the guidance of Dr. Basil C. MacLean, director of Strong Memorial Hospital, Rochester, New York, and Dr. Albert W. Snoke, director of Grace-New Haven Community Hospital, New Haven, Connecticut.

A preliminary study of the Survey reveals that \$88,000,000 was spent in 1946 by the tax-supported and voluntary agencies of Greater Boston, or \$44.65 per capita for the inhabitants of the area. The corresponding average in twenty-nine selected cities

of the country was \$32.48. In the health field \$21.12 was spent per capita in the Boston area as compared with \$14.86 for the same twenty-nine representative cities. In Greater Boston the recipients of these services paid 23.9 per cent of their costs, in the other areas 29.7 per cent.

A question naturally rises that must be answered. Do the greater costs in metropolitan Boston as compared with other areas indicate that a better job is being done here, or that it is being done less efficiently? The survey is expected to find the answer, but it is apparent that in any event economies must be practiced and still greater efficiency achieved if social welfare is to remain solvent.

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 THE JOURNAL OF BONE AND JOINT SURGERY

*The Journal of Bone and Joint Surgery* has this year inaugurated a new plan of publication. Surgeons of the United States of America and the British Commonwealth of Nations are to share, in jointly publishing the *Journal*, the tasks of recording developments in orthopedic surgery.

The *Journal*, formerly a quarterly, now appears in eight issues, four numbers published in Britain alternate with four numbers published, as heretofore, in the United States. The British editorial board includes representatives from the Nations of the British Commonwealth, the American editorial board is composed of representatives of the different sections of the United States.

Through the new co-publication the scope of the *Journal* is extended, a fuller realization of international aim becomes possible. Greater opportunity is anticipated for readers to follow orthopedic developments in a single journal, not only in their own country but throughout the world.

In this larger journal there is increased space for the publication of significant articles, through separate issues national individuality is retained. Clinical and scientific contributions from other countries are welcome, as formerly, and may be found in all issues.

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The percentage breakdown by types of examination and treatment is shown below:

	TYPE	EXAMINATION	TREATMENT
F N T		3%	1%
Pyc		1%	1%
U & Gyn		2%	1%
Heart		1%	1%
Neurological		1%	1%
Orthopedic		1%	1%
Physical Therapy		1%	1%
Psychiatric		1%	1%
Dermatology		1%	1%
T.R.		1%	1%
Neural		1%	1%
Gen. Surg.		1%	1%
Ne. Physiol.		1%	1%
X-Ray & EKG		1%	1%
Laboratory		1%	1%
All Other		1%	1%

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## GREATER BOSTON COMMUNITY SURVEY

OPERATING costs of social and health agencies in the Boston area, paralleling the cost of living in general, have scaled new heights. Deficits are accumulating, and the Greater Boston Community Fund, the Dutch uncle of them all, is feeling the pinch. Established in 1935 to raise funds for 115 agencies in municipal Boston, this super-agency must now provide the sinews of peace for 339 agencies serving fifty-five contiguous communities.

The writing on the wall has become more apparent. As a result of the present disturbing condition the governing boards of the Greater Boston Community Fund and the Greater Boston Community Council early last year invited Robert Cutler, president of the Old Colony Trust Company, to head a committee of citizens to direct a Greater Boston Community Survey of Social and Health Needs and Services.

Mr. Cutler, with no apparent difficulty, persuaded one hundred and eighty out of a panel of one hundred and eighty-four leading citizens to serve on such a committee. In March, 1947, an executive committee of sixteen members was appointed. The field to be covered in the survey has been divided into five divisions, comprising public health, hospitals, recreation and group work, voluntary case-work and statistics and public welfare. The director of the survey is Robert P. Lane, for twelve years executive director of the Welfare Council of New York City. The section on public health is under the direction of Ira V. Hiscock, Sc.D., chairman of the Department of Public Health of Yale University, assisted by Dr. Hugh R. Leavell, professor of public-health practice of the Harvard University School of Public Health, and an advisory group, that on hospitals is under the guidance of Dr. Basil C. MacLean, director of Strong Memorial Hospital, Rochester, New York, and Dr. Albert W. Snoke, director of Grace-New Haven Community Hospital, New Haven, Connecticut.

A preliminary study of the Survey reveals that \$88,000,000 was spent in 1946 by the tax-supported and voluntary agencies of Greater Boston, or \$44.65 per capita for the inhabitants of the area. The corresponding average in twenty-nine selected cities

of the country was \$32.48. In the health field \$21.12 was spent per capita in the Boston area as compared with \$14.86 for the same twenty-nine representative cities. In Greater Boston the recipients of these services paid 23.9 per cent of their costs, in the other areas 29.7 per cent.

A question naturally rises that must be answered. Do the greater costs in metropolitan Boston as compared with other areas indicate that a better job is being done here, or that it is being done less efficiently? The survey is expected to find the answer, but it is apparent that in any event economies must be practiced and still greater efficiency achieved if social welfare is to remain solvent.

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The *Journal*, formerly a quarterly, now appears in eight issues, four numbers published in Britain alternate with four numbers published, as heretofore, in the United States. The British editorial board includes representatives from the Nations of the British Commonwealth, the American editorial board is composed of representatives of the different sections of the United States.

Through the new co-publication the scope of the *Journal* is extended, a fuller realization of international aim becomes possible. Greater opportunity is anticipated for readers to follow orthopedic developments in a single journal, not only in their own country but throughout the world.

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During 1947 28,228 examinations were made by Fee Basis Physicians at a total cost of \$227,793. During the same period 117,788 treatments were given at a cost of \$447,254.

The percentage breakdown by types of examination and treatment is shown below.

TYPE	EXAMINATION	TREATMENT
General	35%	31%
Internal Medicine	25%	16%
Neurological	13%	11 1/2%
Orthopedic	2%	1 1/2%
Physical Therapy	8 1/2%	8 1/2%
Psychiatric	1%	1 1/2%
Dermatology	1%	1 1/2%
T.B.	—	—
Urological	—	—
Gynecology	1 1/2%	1 1/2%
Gen. Physical	4 1/2%	4 1/2%
Neurological	52 1/2%	3 1/2%
Laboratory	14%	14%
All Other	2%	1 1/2%

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E. N. T.	3%	3%
Eye	1 1/2%	1 1/2%
O. T. & C. S.	1 1/2%	1 1/2%
Heart	1 1/2%	1 1/2%
Neurological	1 1/2%	1 1/2%
Orthopaedic	1 1/2%	1 1/2%
Physical Therapy	1 1/2%	1 1/2%
Psychiatric	1 1/2%	1 1/2%
Dermatologist	1 1/2%	1 1/2%
General	1 1/2%	1 1/2%
Gen. Phys. & Surg.	1 1/2%	1 1/2%
Gen. Phys. & Surg.	1 1/2%	1 1/2%
Lab. & EKG	1 1/2%	1 1/2%
Laboratory	1 1/2%	1 1/2%
All Other	1 1/2%	1 1/2%

On the first of November a new Fee Schedule became effective as a result of an agreement between the Massachusetts Medical Society and the Veterans Administration. Certain fees may not be entirely adequate, however. The Medical Society is presently negotiating for increases where indicated.



A Board of Review has been established by the Medical Society to which private physicians and the Veterans Administration may present their problems regarding veterans' care, and already have handled and adjudicated many cases satisfactorily.

On the whole the year has been marked by better relations between the private physicians and the Veterans Administration. Most physicians have been very patient and understanding, with regard to the problem confronting the Veterans Administration during a year of tremendous expansion and their practical suggestions, freely given have contributed to a great extent to the evolution of a sounder and more efficient Veterans' Care Program.

Officials of the Massachusetts Medical Society deserve much credit for many hours of devoted work, in solving problems of policy and procedure, and in liaison with the Veterans Administration.

STEPHEN J. DALTON, M.D., *Medical Director*

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Textbook of the Ear, Nose and Throat* By Francis L. Lederer, M.D., professor and head, Department of Otolaryngology, University of Illinois College of Medicine, chief, Otolaryngological Service, Research and Educational Hospital, and director of education and chief of the Ear, Nose and Throat Service, Illinois Eye and Ear Infirmary, and Abraham R. Hollender, M.Sc., M.D., attending otolaryngologist, St. Francis Hospital, Miami Beach, Florida. Second edition. 8°, cloth, 596 pp., with 182 illustrations. Philadelphia: F. A. Davis Company, 1947. \$7.00.

This textbook, written primarily for students, first published in 1942, and reprinted in 1943 and 1944, has been revised to include recent advances in the subject, especially in the field of chemotherapy and antibiotics. The material is well organized, and the text well written and printed with a good, readable type. The illustrations are excellent. The volume is recommended for medical libraries.

*Illustrations of Regional Anatomy* By E. B. Jamieson, M.D. Seven sections. Seventh edition. 8°, paper, 320 plates. Baltimore: Williams and Wilkins Company, 1947. \$20.00.

This compendium of regional anatomy, first published in 1934, has been corrected in this seventh edition. The set has evidently filled a need in anatomic teaching, since all the editions have been exhausted comparatively soon after publication. The illustrations are in color and without text. The plates were printed in Great Britain and bound in the United States.

*Physical Medicine in General Practice* By William Bierman, M.D., attending physical therapist, Mount Sinai Hospital, and assistant clinical professor of medicine, Columbia University College of Physicians and Surgeons. With a chapter on medical rehabilitation by Dr. Sidney Licht. Second edition, revised and enlarged. 8°, cloth, 686 pp., with 310 illustrations. New York: Paul B. Hoeber, Incorporated, 1947. \$8.00.

Dr. Bierman, in this second edition of his treatise, first published in 1944, has revised the text to incorporate advances in knowledge in the field of physical medicine. Included in the new material are the combination of penicillin and fever therapy in the treatment of syphilis and early ambulation in various medical and surgical conditions. The first fifteen chapters deal with the various special means of therapy, including heat and cold and hydrotherapy, climatotherapy, sun, infrared and ultraviolet radiation, diathermy, fever therapy, massage, exercise and occupational therapy, and special chapters on medical rehabilitation and the conduct of treatments. The remaining chapters discuss the diseases

and conditions of the systems of the body, amenable to treatment by physical means. A list of selected references is appended to each chapter. An appendix is devoted to apparatus. A good index concludes the volume. The text is printed with a good type, on good paper.

*Conference on Metabolic Aspects of Convalescence. Transactions of the thirteenth meeting, Naushon Island, Woods Hole, Massachusetts, June 10, 11, 1946.* 8°, paper, 232 pp., with 67 illustrations and 26 tables. *Transactions of the fourteenth meeting, New York, November 12, 13, 1946.* 8°, paper, 190 pp., with 78 illustrations and 12 tables. New York: The Conference, 1947. Thirteenth meeting \$2.00 per copy. Fourteenth meeting \$2.25 per copy.

These two volumes of proceedings contain the papers read at the conferences held in 1946. The fourteenth meeting was featured by a symposium on bone metabolism. The other papers discussed various aspects of the subject. The thirteenth volume contains an index of contents of all the previous volumes and also a list of libraries where complete sets of the proceedings have been deposited. There are three sets in Boston — at the Boston Medical Library, the Harvard Medical School and the Massachusetts General Hospital. The volumes should be in all medical libraries.

*Diseases of the Nervous System* By W. Russell Brain, D.M. (Oxon), F.R.C.P. (London), physician to the London Hospital and to the Maida Vale Hospital for Nervous Diseases. Third edition. Oxford Medical Publications. 8°, cloth, 987 pp., with 79 illustrations. London: Oxford University Press, 1947. \$10.75.

This new edition of a standard work, first published in 1933, and last revised in 1942, has again been revised to include information gained during World War II. A chapter on nutritional disorders of the nervous system and sections on equine encephalitis, the nervous complications of epidemic hepatitis, myelopathy, spinal radiculitis and platybasia have been added. The section on aphasia has been rewritten, including material on disorders of the body image. Material has been added on chemotherapy, including the use of penicillin in meningitis and neurosyphilis, costoclavicular syndromes, herniated lumbar intervertebral disks, bronchial neuritis and the neurology of the lipodoses. The last section on the psychologic aspects of neurology includes two new sections on the status of psychogenic symptoms and psychotherapy and on psychometric tests. Lists of selected references are appended to each disease or section of the text. The type and printing are excellent, but the use of a heavy, filled paper makes the volume too heavy for its size. The book should be in all medical libraries.

*The Louse. An account of the lice which infest man, their medical importance and control.* By Patrick A. Buxton, C.M.G., F.R.S., director, department of medical entomology, London School of Hygiene and Tropical Medicine, and professor of medical entomology, University of London. Second edition. 8°, cloth, 164 pp., with 47 illustrations and 14 tables. Baltimore: Williams and Wilkins Company, 1946. \$3.25.

This British monograph, first published in 1941, has been revised to include the advances in knowledge of the subject since the publication of the first edition. The volume is well published and should be in all medical and public-health libraries.

*Practical Emulsions* By H. Bennett, technical director, Glyco Products Company, Inc., and editor, *Commercial Waxes, Chemical and Technical Dictionary, Chemical Formulary* and a so forth. Second, completely revised edition, including a symposium on *Emulsifying Agents and Emulsions in Industry*. 8°, cloth, 568 pp. Brooklyn, New York: Chemical Publishing Company, Incorporated, 1947. \$8.50.

This new edition of an authoritative technical treatise has been carefully revised and brought up to date. Material has been added on partial fatty-acid esters of polyhydric alcohols and their application to food products and also special sections on the use of soap, lecithin and pectin as emulsifying agents and surface-active germicides. A symposium on

industrial emulsions has been added including their use in leather synthetic latex polishes cosmetics, paints, dyeing and coloring. New formulas have been included in the appropriate section. In this section the chapters on cosmetics and drug emulsions food emulsions and medicinal emulsions are of medical interest. A good index concludes the text. The book is well printed with a good type but the use of heavy coated paper is to be deplored in a volume without illustrations. The book is recommended as a reference source on its subject.

*Therapeutics of Infancy and Childhood*. Edited by Harry R. Litchfield M.D., consultant in pediatrics Rockaway Beach Hospital Rockaway Beach New York attending pediatrician Beth El Hospital, Brooklyn Women's Hospital and Brooklyn Thoracic Hospital and chief in pediatrics East New York Dispensary Brooklyn and Leon H. Dembo M.D. visiting pediatrician St. Luke's and St. Ann's hospitals and consulting pediatrician Polyclinic Hospital, Cleveland Third edition. 5 volumes illustrated 8, cloth, desk index 148 pp. vol. 1 869 pp., vol. 2, 825 pp. vol. 3 750 pp. and vol. 4 829 pp. Philadelphia F. A. Davis Company 1947 \$40.00

This popular system first published in 1942 has been revised to bring the subject matter up to date since the publication of the previous edition in 1945. The work is the joint effort of one hundred and twenty six contributors specialists in their particular fields. The subject matter is classified by the systems of the body and by topics and is preceded by material of a general character. The chapter on chemotherapy has been largely rewritten and the sections on antibiotic treatment, including penicillin and streptomycin have been amplified. The material on cystic fibrosis of the pancreas celiac disease rheumatic fever Rh factor allergy and folic acid has been revised to date. The present-day treatment of virus pneumonia, toxoplasmosis and the dysenteries is presented in its practical aspects. A comprehensive index of a hundred and forty-eight pages constitutes a separate volume. The work is well published in every way. The type printing and paper are excellent. The volumes are comparatively light for their size. The production is a credit to the publisher. The work is recommended for all medical libraries and should prove valuable as a reference source for physicians with children as their patients.

## NOTICES

### ANNOUNCEMENT

Dr. Milton H. Rodofsky announces the opening of an office for the practice of psychiatry at 341 Beacon Street Boston

### GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday April 20 at 8:15 p.m. A symposium entitled "The Acute Abdomen" will be presented.

The Acute Abdomen in Pediatric Practice Dr. Henry W. Hudson Jr.  
The Acute Abdomen in Adult Practice Dr. Claude E. Welch  
Discussion Drs. Charles B. Mixer and Jacob Fine

### SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association 554 Columbus Avenue Boston on Tuesday April 20 at 12 noon. Dr. Norman A. Welch will speak on "The Evaluation of Some of the Modern Types of Therapy". Physicians are cordially invited to attend.

### SUFFOLK DISTRICT MEDICAL SOCIETY

The spring dinner of Suffolk District Medical Society will be given at the Harvard Club 374 Commonwealth Avenue Boston, on Saturday May 1. Cocktails will be served at

6:30 and dinner at 7:00 p.m. Mr. Gerald G. Gross editor *Washington Report on the Medical Sciences* will speak on the subject "The Prospects for Federal Medical Legislation which will be discussed by Drs. Elmer S. Bagnall and Allan M. Butler.

The ladies and members of the Massachusetts Medical Society are cordially invited. Tickets cost \$4.00 and must be purchased in advance from Dr. Richard S. Eustis 319 Longwood Avenue Boston 15 Massachusetts. Dress is optional.

### AMERICAN GYNECOLOGICAL SOCIETY

A meeting of the American Gynecological Society will be held at the Williamsburg Restoration Incorporated, Williamsburg Virginia, on May 24-25 and 26.

### AMERICAN LARYNGOLOGICAL ASSOCIATION

The sixty ninth annual meeting of the American Laryngological Association will be held at the Homestead Hotel Springs Virginia on April 14 and 15.

Members of the medical profession are cordially invited.

### AMERICAN RADIUM SOCIETY

The annual meeting of the American Radium Society will be held at the Stevens Hotel Chicago on June 20 and 21. Refresher courses and panel discussions will be presented, and the Janeway Lecture will be delivered by Sir Stanford Cade attending surgeon Westminster and Mt. Vernon Hospitals and the Radium Institute of London. His subject will be "The Achievement of Radium in the Fight Against Cancer."

Further details regarding the program may be obtained from the secretary Dr. Hugh F. Hare 605 Commonwealth Avenue Boston 15.

### SOUTHERN SURGICAL ASSOCIATION

The annual meeting of the Southern Surgical Association will be held at The Greenhner White Sulphur Springs, West Virginia on December 7-8 and 9 (secretary, Alfred Blalock M.D. The Johns Hopkins Hospital Baltimore 5 Maryland).

### AMERICAN PHYSIOTHERAPY ASSOCIATION

The annual conference of the American Physiotherapy Association will be held at the LaSalle Hotel, Chicago from May 23 to 28.

### ARIZONA STATE MEDICAL ASSOCIATION

The annual meeting of the Arizona State Medical Association will be held in Phoenix from May 19 to 21 (secretary Frank J. Milloy, M.D., 15 East Monroe Street, Phoenix Arizona).

### HAWAII TERRITORIAL MEDICAL ASSOCIATION

The annual meeting of the Hawaii Territorial Medical Association will be held in Honolulu from May 6 to 9 (secretary, H. L. Arnold Jr., M.D., Mabel Smyth Building Honolulu 53 Hawaii).

### ILLINOIS STATE MEDICAL SOCIETY

The annual meeting of the Illinois State Medical Society will be held in Chicago from May 10 to 12 (secretary Harold M. Camp M.D., 224 South Main Street Monmouth Illinois).

### KANSAS MEDICAL SOCIETY

The annual meeting of the Kansas Medical Society will be held in Wichita from May 10 to 13 (secretary D. D. Vermlison M.D., 512 New England Building Topeka Kansas).

## NEBRASKA STATE MEDICAL ASSOCIATION

The annual meeting of the Nebraska State Medical Association will be held in Lincoln from May 3 to 6 (secretary, R. B. Adams, M.D., 416 Federal Securities Building, Lincoln 8, Nebraska)

## NEW HAMPSHIRE MEDICAL SOCIETY

The annual meeting of the New Hampshire Medical Society will be held at the Hotel Wentworth, Newcastle, New Hampshire, on June 2 and 3 (secretary, Carleton R. Metcalf, M.D., 5 South State Street, Concord, New Hampshire)

## MEDICAL SOCIETY OF THE STATE OF NEW YORK

The annual meeting of the Medical Society of the State of New York will be held in New York City from May 17 to 21 (secretary, W. P. Anderson, M.D., 292 Madison Avenue, New York City)

## MEDICAL SOCIETY OF THE STATE OF NORTH CAROLINA

The annual meeting of the Medical Society of the State of North Carolina will be held in Pinehurst from May 3 to 5 (secretary, Roscoe D. McMillan, M.D., P. O. Box 232, Red Springs, North Carolina)

## RHODE ISLAND MEDICAL SOCIETY

The annual meeting of the Rhode Island Medical Society will be held in Providence on May 12 and 13 (secretary, Morgan Cutts, M.D., 155 Thayer Street, Providence 6, Rhode Island)

## SOUTH CAROLINA MEDICAL ASSOCIATION

The annual meeting of the South Carolina Medical Association will be held in Charleston from May 12 to 14 (secretary, Julian P. Price, M.D., 105 West Cheves Street, Florence, South Carolina)

## WEST VIRGINIA STATE MEDICAL ASSOCIATION

The annual meeting of the West Virginia State Medical Association will be held in Huntington from May 10 to 12 (secretary, Mr. Charles Lively, Box 1031, Charleston 24, West Virginia)

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 15

## THURSDAY, APRIL 15

12 00 m Clinicopathological Conference Nurses Home Allerton Hospital Brookline

## FRIDAY, APRIL 16

\*9 00-10 00 a.m. Certain Renal Complications in Diabetes Dr. George V. Mann Joseph H. Pratt Diagnostic Hospital  
\*10 00 a.m.-12 00 m. Medical Staff Rounds Peter Bent Brigham Hospital

## TUESDAY, APRIL 20

\*12 00 m. South End Medical Club  
\*12 00 m. X-ray Conference Margaret Jewett Hall Mt. Auburn Hospital Cambridge  
\*12 15-1 15 p.m. Clinicorontgenological Conference Peter Bent Brigham Hospital  
\*1 30-2 30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital  
8 15 p.m. Greater Boston Medical Society Beth Israel Hospital Auditorium

## WEDNESDAY, APRIL 21

\*9 00-10 00 a.m. Recent Advances in Anesthesia Dr. Philip S. Marcus Joseph H. Pratt Diagnostic Hospital  
\*12 00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital  
\*2 00-3 00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater, Children's Hospital

\*Open to the medical profession

APRIL 2-30 Joseph H. Pratt Diagnostic Hospital Medical Conference Program Page 492 issue of April 1

APRIL 10 American Congress of Physical Medicine Page 344 issue of March 4

APRIL 12 Harvard School of Public Health Page 384, issue of March 11

APRIL 12 and 13 American Otolological Society Page 492 issue of April 1

APRIL 13 Harvard Medical Society Page 455 issue of March 2

APRIL 13 New England Society of Anesthesiologists Page 453 issue of March 25

APRIL 14 New England Dermatological Society Page 455 issue of March 25

APRIL 14 and 15 American Laryngological Association Page 543

APRIL 15 Berkshire District Medical Society Page 492, issue of April 1

APRIL 19-23 American College of Physicians Page xiii issue of July 31

APRIL 20 Greater Boston Medical Society Page 543

APRIL 20 South End Medical Club Page 543

APRIL 26-29 American Dermatological Association Page 456 issue of March 25

APRIL 29-MAY 2 American Academy of Pediatrics Page 240 issue of February 12

APRIL 30 and MAY 1 American Gastro-Enterological Association Page 456 issue of March 25

MAY 1 Suffolk District Medical Society Page 543

MAY 3 American Society for Clinical Investigation Page 456 issue of March 25

MAY 3 and 4 Association of American Physicians Page 492, issue of April 1

MAY 4 and 5 Association of Military Surgeons of the United States Page 456 issue of March 25

MAY 6 Suffolk Censors' Meeting Page 344, issue of March 4

MAY 6-8 American Association for the Study of Gonorrhea Page xiii issue of July 31

MAY 9-14 American Psychiatric Association Page 492, issue of April 1

MAY 12-14 American Association of Genito-Urinary Surgeons. Skytop Lodge, Skytop, Pennsylvania

MAY 13 Indications for the Use of Forceps. Dr. Roy J. Heffernan. Pentucket Association of Physicians 8 30 p.m. Haverhill

MAY 16-22 American Board of Obstetrics and Gynecology, Inc. Page 344 issue of March 4

MAY 16-23 International College of Surgeons Page 136 issue of January 22

MAY 17-19 American Ophthalmological Society Page 492 issue of April 1

MAY 17-20 American Urological Association Hotel Statler Boston

MAY 17-20 Association for the Study of Internal Secretions. Page 492 issue of April 1

(Notices concluded on page xv)

The *Journal* lacks extra copies of the January 1 and February 19, 1948, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the *Journal* will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15)

## NOTICES (Concluded from page 541)

- May 18-22. American Association on Mental Deficiency. Copley Plaza Hotel, Boston.
- May 20-25. American Board of Ophthalmology. Page 170. Issue of January 29.
- May 23-28. American Physiotherapy Association. Page 543.
- May 24-26. American Gynecological Society. Page 543.
- May 25-27. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
- May 27-29. American Surgical Association. Page 455. Issue of March 25.
- June 7-10. National Gastroenterological Association. Page 455. Issue of March 25.
- June 17-20. American College of Chest Physicians. Page 455. Issue of March 25.
- June 20 and 21. American Radium Society. Page 543.
- June 21 and 22. American Society for the Study of Sterility. Page 384. Issue of March 11.
- June 25 and 26. Christian Medical Society. Page 492. Issue of April 1.
- June 28-30. American Academy of Pediatrics. Hotel Schroeder, Milwaukee, Wisconsin.
- July 6-24. Students International Clinical Congress. Page 455. Issue of March 25.
- July 12-17. First International Poliomyelitis Conference. Page 49. Issue of January 1.
- August 11-21. International Congress on Mental Health. Page 344. Issue of March 4.
- August 23-26. International Society of Hematology. Page 419. Issue of March 18.
- August 26-28. American Association of Blood Banks. Page 420. Issue of March 18.
- September 13-15. American Academy of Pediatrics. Olympic Hotel, Seattle, Washington.
- September 20-23. American Hospital Association. Page 310. Issue of February 26.
- September 29. Mississippi Valley Medical Editors Association. Page 170. Issue of January 29.
- October 6-9. American Board of Ophthalmology. Page 170. Issue of January 29.
- November 8-12. American Public Health Association. Page 420. Issue of March 18.
- November 20-23. American Academy of Pediatrics. Annual Meeting. Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey.
- December 7-9. Southern Surgical Association. Annual Meeting. Page 545.

## DISTRICT MEDICAL SOCIETIES

## BIRMINGHAM

April 15. Annual Meeting. Willma Inn, Willma, Ala.

## FRANKLIN

May 11. Annual Meeting. Hotel Weldon, Greenfield.

## MIDDLESEX EAST

May 12. Annual Meeting. Bear Hill Golf Club, Wakefield.

## PLYMOUTH

April 15. State Farm Bridgewater.  
May 20. Lakeville Sanatorium, Lakeville.

## SUFFOLK

May 1. Spring Dinner.  
May 6. Censora Meeting.

## WORCESTER

April 14. Worcester Mahanoma Hospital.  
May 12. Annual Meeting.

Medical Advertisement



From where I sit  
by Joe Marsh

## Will's Proud of His Big Ears

*Will Dudley's mighty proud of his big ears! Best crop of corn he's grown since '38. And Will, like so many other farmers, has plenty of reason to be proud of what he raises.*

The farmer has always been a key-stone in our economic life, and the key to our national well-being. But from where I sit, he's more important now than ever. He's not only feeding America—but friends of America overseas—building good will for this country at a time when friendship for democracy is most important.

*And farmers have willingly shouldered that responsibility. Will spends extra hours in his cornfield, comes home tired to a temperate glass of beer and early bed, to be ready for the next day's work.*

From where I sit, America can be mighty grateful for her five million farmers for their productivity, hard work, temperate living—of which Will's moderate glass of beer is proof!

*Joe Marsh*

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# The New England Journal of Medicine

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Number 16

## ORTHOPEDIC APPLIANCES IN THE REHABILITATION OF PATIENTS WITH SPINAL-CORD INJURIES\*

DONALD S. BICKERS, M.D.†

BOSTON

A REVIEW of the literature dealing with the orthopedic treatment of spinal-cord injuries is remarkable chiefly for the scarcity of available reference. This deficiency is easily understandable in view of the fact that it was only with the advent of World War II that the medical profession was faced with the problem of treatment of a large group of patients with these injuries. Such cases occur sporadically in civilian life, but it is unusual for a large number to be grouped on a service devoted entirely to the treatment of problems peculiar to this type of injury. A considerable number of spinal-cord injuries, with resulting paraplegia, were incurred in World War I, but survival was the exception rather than the rule. The average length of life after such injuries is reputed to have been approximately three weeks, death being due in the majority of cases to sepsis in patients who survived initial shock. With the advent of chemotherapy, air evacuation and improved methods of treatment of shock, a high percentage of such casualties in World War II were saved for rehabilitation to a useful life. Most references and standard texts on orthopedic appliances have only an indirect bearing since they are concerned with allied but not identical problems. The long, double upright brace for the leg is discussed by Jordan,<sup>1</sup> but the concern is primarily with its use as a weight-bearing appliance rather than one designed only for splinting action as it is used in the treatment of paraplegic patients. A direct reference in the recent literature is that of Kuhn,<sup>2</sup> who mentions the brace problem in a general review of the care of such cases.

The problems presented by the paraplegic patient are unique in many ways, and one of the most important is that of braces. Proper bracing is the cornerstone on which the ambulation program is built, and ambulation plays a vital part in any compre-

hensive program designed to return such a patient to his rightful place in society. Before the factors involved in choosing the proper brace for an individual case are considered, it is necessary to establish the point in the patient's progress where braces are indicated. This turning point marks the transition from the wheelchair mobility to ambulation requiring full use of all remaining voluntary muscular power. On the Neurosurgical Service, Cushing Veterans Administration Hospital, organized generally along the lines of the Munro classification, braces are not fitted until the patient has entered Stage III. In Stage I (spinal shock), emphasis is placed on the treatment of the original injury, treatment and prevention of decubitus ulcers, bladder care, maintenance of good nutrition and intensive physiotherapy. In Stage II (diagnostic and reparative surgery) surgical procedures indicated in complications frequently incident to spinal-cord injuries are carried out. At that time, surgical closure of decubitus ulcers is done, and necessary genito-urinary surgery is completed. Bladder training, designed to give the patient twenty-four-hour bladder control, is carried on simultaneously and is usually completed at the end of this stage. In cases in which deformities develop despite all preventive measures, corrective orthopedic procedures are carried out. Of equal importance to future efficient ambulation are neurosurgical procedures designed to relieve uncontrolled muscle spasm. The importance of the proper treatment of spasm has been pointed out by a number of investigators and cannot be overemphasized. The paraplegic patient, deprived of most or all of his postural reflexes,<sup>3</sup> must develop through prolonged instruction and practice a new system of balance maintenance. This system is based on voluntary changes of posture designed to distribute body weight equally around the vertical axis of the skeletal system. The art of balance maintenance in sitting and standing is the first and basic phase of ambulation training, and upon its acquisition depends the entire success of subsequent ambulation instruction. The spasm of an even

\*From the Paraplegia Section, Neurosurgical Service, Cushing General Hospital (now Cushing Veterans Administration Hospital).

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moderately well developed mass reflex, particularly in injuries of the thoracic and cervical cord, renders this goal unattainable. The sudden, unpredictable stretch reflexes cause flexion or extension

plegic patients, frequently result when braces are forced on a markedly spastic subject. Evaluation of numerous agents and procedures for relief of spasm employed on 200 patients treated on this

TABLE 1 Correlation between Injury Level, Resulting Muscle Deficit and Indicated Type of Brace  
(Adapted from Morris<sup>6</sup>)

APPROXIMATE CORD SEGMENTS	MUSCLE GROUP	CHIEF MUSCLES	SEGMENTAL INNERVATION	TYPE OF BRACE
C1-T1	Neck All movements	All muscles	XI C1-C8	Same except for additional special upper-extremity braces
	Pectoral girdle All movements	All muscles	C3-C8	
	Arm flexion	Coracobrachialis Biceps Brachialis	C6-C7 C5-C6 C5-C6	
	Arm, extension	Triceps Anconeus	C6-C8 C7-C8	
	Forearm and hand All movements	All muscles	C6-T1	
T1-T6	Thoracic cage Extension — lateral Flexion	Intercostals Longissimus dorsi Iliocostalis dorsi Spinalis dorsi	T1-T12 T1-T12 T1-T12 T6-T9	
	Pelvis and lumbar spine Flexors	Rectus abdominis External oblique Internal oblique Transversus abdominis	T6-T12 T6-T12 T10-L1 T7-L1	
L1-L4 (5)	Pelvis and lumbar spine Extensors, also act as lateral flexors	Iliocostalis lumborum Longissimus dorsi Quadratus lumborum	L1-L4 L1-L5 L1-L4	
	Thigh, flexors	Psoas major and minor Iliacus Sartorius Quadriceps femoris	L1-L4 L2-L4 L3-L4 L3-L4	
L4-S3	Thigh, extensors	Gluteus maximus Biceps femoris Semitendinosus Semimembranosus	L5-S2 S1-S3 L5-S2 L4-S1	Long leg brace with back brace
	Thigh Internal rotators	Pyriformis Gluteus minimus Pectineus	S1-S2 L4-S1 L2-L3	Long leg brace with pelvic band
	Thigh External rotators	Gluteus maximus Obturator internus Obturator externus Quadratus femoris Tensor fasciae latae	L5-S2 L5-S2 L3-L4 L4-S1 L4-S1	Long leg brace
	Thigh Adductors	Adductor magnus Adductor longus Pectineus Gracilis	L3-L5 L2-L3 L2-L3 L2-L4	
	Thigh Abductors	Pyriformis Gluteus medius Gluteus minimus Tensor fasciae latae	S1-S2 L4-S1 L4-S1 L4-S1	
	Leg Flexors	Biceps femoris Semitendinosus Semimembranosus Sartorius	S1-S3 L5-S2 L4-S1 L2-L3	
	Leg, extensors	Quadriceps femoris	L3-L4	Double upright drop-foot brace with drop-foot spring
	Foot, plantar flexors	Gastrocnemius Soleus	S1-S2 L5-S2	
	Foot inverters	Flexor digitorum longus Flexor hallucis longus Tibialis posterior	L5-S1 L5-S2 L5-S1	
	Foot, dorsiflexors	Tibialis anterior Extensor digitorum longus Extensor hallucis longus Peroneus longus Peroneus brevis Peroneus tertius	L4-S1 L4-S1 L4-S1 L4-S1 L4-S1 L4-S1	Wire drop-foot brace

of the lower extremities and trunk, with precipitate loss of balance. The result is either a fall or a rescue by the instructor, which offers a psychologic and mechanical hindrance to ambulation progress. Decubitus ulcers, an ever-present threat in para-

service over the past year indicate that the treatment of choice is the anterior rhizotomy described by Munro.<sup>4</sup> With proper indications, complete rhizotomy is done on complete cord lesions, and differential rhizotomy is done on partial cord lesions.

With these complications successfully treated, the patient is passed to Stage III (wheel-chair ambulation). It is in this relatively brief stage that the patient must first be measured for braces. Premature measurement may result in needless expense in brace alterations occasioned by changes in the nutritional status during Stages I and II. A contour tracing is made of the parts to be braced with the patient lying on a flat surface and supplemented by circumferences of extremities and trunk. The prescribed brace is then given to the patient, and he is instructed in its application in bed. When this is learned together with other basic elements of self-care, the patient is deemed ready for beginning ambulation training.

A basic premise must be borne in mind regarding the factors involved in choosing the proper brace for a given patient: the function of the brace is not the support of body weight but the maintenance of normal postural relations through splinting action. In effect, the muscle groups responsible for maintaining the body in an erect, stable position are replaced by external mechanical supports, with maximum retention of normal joint function. Three chief factors may be mentioned. The first is the level of the injury, which is usually the most important single criterion for determining the type of brace that the patient will need. When the optimal stage for brace fitting described above has been reached, there is usually a close correlation between the level of injury and the type of brace indicated. Unless otherwise indicated, all levels in the following discussion are dermatome levels. A summary of these data is presented in Table 1. In most cases the type of brace needed may be accurately determined in advance by careful muscle analysis to ascertain the existing deficit. Such tests should be done at regular intervals during the course of rehabilitation as an index of improvement, particularly in partial lesions of the cord and cauda equina. Minor variations may be indicated, and the patient must be observed in all phases of ambulation training for a proper decision to be reached. These are usually variations on a single category of brace rather than between categories — such as changes in the construction of back brace. The second factor is the severity of the injury: whether a partial or complete lesion of the cord or cauda equina. Selection of braces for complete lesions is relatively simple, but partial lesions present a greater problem since the level of injury cannot be closely correlated with the type of brace indicated. For example, a patient with a partial cord lesion at the fifth cervical segment may require a double upright leg brace with a drop-foot spring on the right, and a simple wire drop-foot brace on the left. These situations must be met individually on the basis of thorough muscle analysis and clinical observation of the patient in ambulation, the appliance that most nearly replaces the existing deficit is then chosen. The third con-

sideration comprises malformations that may be present. Most of them will be prevented or corrected surgically during the first three stages of rehabilitation, but prolonged conservative therapy may be the treatment of choice. After relief of spasm, mild hip contractures and scolioses, to mention two examples, may demand some special brace to permit corrective exercises and ambulation. These occasional complications seldom change the overall requirements of a given patient but can be met with adjustments within a basic brace pattern.

#### TYPES OF BRACES

##### *Drop-Foot or Short Leg Brace (Fig. 1)*

The specifications for the drop foot brace are as follows:

*Wire drop-foot brace.* Upright supports of 22-gauge spring steel wire are attached to the shoe, with a lightweight stirrup or pinion through the

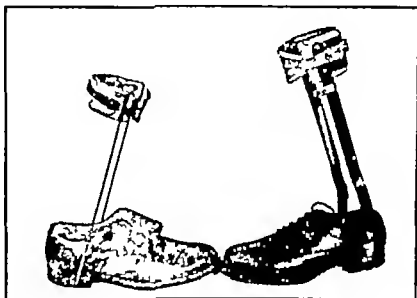


FIGURE 1 *Wire Drop-Foot Brace (Left) Double Upright Drop-Foot Brace (Right)*

heel. The calf band is of 17-gauge spring steel, with  $\frac{3}{8}$ -inch sheet of sponge-rubber padding, covered with a calf-skin, single strap and buckle. The weight of the brace with a shoe is 1 pound, 12 ounces, and the total weight is 3 pounds, 8 ounces.

*Double upright drop-foot brace.* Steel uprights,  $\frac{5}{8}$  by  $\frac{3}{8}$ -inch, are used, with a calf band and strap similar to that of the wire drop-foot brace. A drop-foot spring is applied across a semihinged-type ankle joint, stirrup shoe attachment. The weight of the brace with a shoe is 3 pounds, and the total weight is 6 pounds.

*Indications.* Analysis of the muscles involved in control of the foot (Table 1) indicates that loss of function below the knee results from an injury to the lowest lumbar cord segments, conus or cauda equina, or all three, that involves all or part of the fourth



lumbar through the second sacral segments. Paralysis of this type are almost invariably flaccid, with considerable muscle atrophy due to damage of either the anterior-horn cell in the fourth lumbar through the second sacral segments, or to transections of all or part of the filaments of the cauda equina. Spasm is rarely a problem. This injury has been most frequently seen in patients with partial lesions of the conus and cauda secondary to penetrating

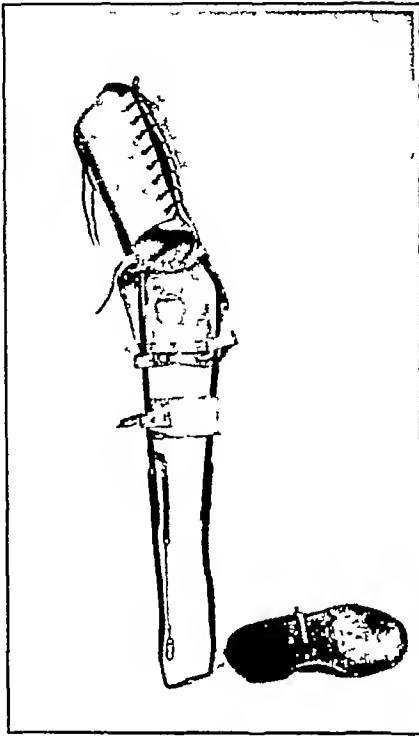


FIGURE 2 *Caliper Long Leg Brace with Detachable Drop-Foot Spring*  
Note instep bar and removable slotted plate.

wounds at or below the first lumbar vertebra. In such involvement, the function of the brace is to substitute a compensatory force for the lost dorsiflexors of the foot and, if necessary, to stabilize the ankle. The loss of the tibialis anterior, extensor digitorum longus and extensor hallucis longus will result in a drop foot with little change in ankle stability (Table 1). Such patients are adequately supported with the wire drop-foot brace, since no lateral stabilization of the ankle is required. In cases in which there is complete loss of all muscle activity below the knee, stabilization of the ankle is desirable, since such activity is normally chiefly dependent on the interaction of the muscle groups of the lateral and posterior aspects of the leg. This is best done with the double upright drop-foot brace, which provides good bilateral support of the ankle joint and positive spring drop-foot correction. In an effort to reduce the weight of the brace, the medial upright support was omitted experimentally.

The resulting abduction and eversion deformity of the foot with incomplete ankle stabilization caused us to discontinue its use. It is mentioned only for the sake of completeness and condemnation.

#### *Long Leg Braces (Fig 2 and 3)*

The specifications of long leg braces are as follows:

*Caliper with detachable drop-foot spring* Uprights,  $\frac{5}{8}$  by  $\frac{3}{16}$  inch, steel drop-ring lock, a hinged knee joint and calf and thigh bands of 17-gauge spring steel, padded with  $\frac{3}{16}$ -inch sheet sponge rubber, covered with calfskin. The ankle joint is a caliper with a detachable drop-foot spring. The drop-foot spring, with the standard attachment above, is attached below to a steel instep bar,  $\frac{3}{16}$  by  $\frac{3}{8}$  inch, by means of a detachable slotted plate fitting over a button forged on the

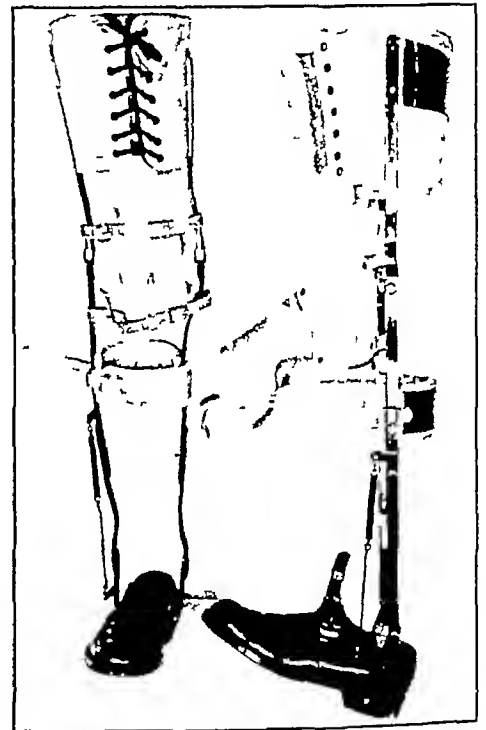


FIGURE 3 *Long Leg Brace with Hinged Ankle Joint and Stirrup Attachment*  
Drop-Foot Spring and Shoe Permanently Attached

end of the instep plate. The weight of each brace with a shoe is 5 pounds, 8 ounces, and the total weight of both braces with shoes is 11 pounds.

*Long leg brace with hinged ankle joint and stirrup attachment* Uprights,  $\frac{5}{8}$  by  $\frac{3}{16}$  inch, steel hinged knee joint, with a drop-ring lock. Calf and thigh bands are of 17-gauge spring steel padded with  $\frac{3}{16}$ -inch sheet sponge rubber, covered with calfskin, the drop-foot spring is permanently attached above and below on either side of a semi-hinged ankle joint. The weight of the brace with a shoe is 5 pounds, 8 ounces, and the total weight is 11 pounds.

**Indications** The chief single indication for this type of brace is loss of stability of the knees. This added factor marks the distinction between the functions performed by this brace and those of the double upright drop-foot brace. The ability to maintain the legs in extension and consequently to maintain the body in erect posture is directly dependent upon the integrity of the quadriceps femoris muscle (Table 1). Should muscle analysis and the clinical test of having the patient stand erect indicate that the activity of the muscle is lost or so weakened as to render extension of the leg inadequate, this function must be replaced by the long leg brace. These lesions occur predominantly in the lumbar cord segments, but may be due to severe or complete transections of the cauda equina at or below the level of the third lumbar vertebra. Any remaining flexors of the leg are necessarily denied their normal action at the knee by the locked knee joint and are not of primary importance in determining the type of brace used for injuries of this level. Their importance, as is any remaining function of the quadriceps femoris muscle, is in determining the type of gait the patient will use. This brace enables the patient with complete or partial loss of function from the third lumbar through the fifth sacral segment to stand erect and subsequently to learn the gait best suited to his injury. The two types of long leg brace are presented because of their relative merits and disadvantages. The first, with a detachable drop-foot spring, was devised in an effort to overcome the difficulties imposed by the caliper-stop brace while retaining the advantage of a detachable shoe. The caliper-stop brace, particularly with heavier patients and those actively engaged in ambulation, is often subject to having the drop foot recur owing to posterior bending of the stops. All the ambulation gaits, particularly the swing through, tend to cause forcible plantar flexion of the foot, stress being exerted on the stops. Similar tension is exerted when the patient ascends stairs and other obstacles, when during the course of the ascent, the toe of the foot is caught temporarily under a protruding ledge. The detachable drop-foot spring is fastened permanently above but is attached below by the slotted plate to the protruding button on the shoe after the calipers are inserted. The positive tension exerted by the properly adjusted drop-foot spring allows normal plantar flexion of the foot and has proved more effective than stops in correcting the drop foot. The spring should be parallel to its supporting lateral upright to reduce the tendency to eversion and abduction of the foot, which may result if the mechanical advantage is too great. Furthermore, the spring must be properly adjusted to prevent over-correction. The chief advantages derived are the convenience in application and removal, without the necessity of removing the shoes, and continued drop-foot correction. The advantage of the second type of brace is the slight increase in

lateral stability of the ankle with the same good drop-foot correction. The hinge may be so constructed as to allow plantar flexion of the feet. The obvious disadvantage of this brace is the greater difficulty of application and removal and the necessity for removing shoes and braces simultaneously. In the use of either of these braces, three points of clinical importance should be emphasized. The hinged ankle joint should be placed 1 cm. above the tip of the lateral malleolus in line with the transverse axis of the talotibial joint. The knee joint should be placed opposite the midpoint of the medial and lateral condyles of the femur (the points of emergence of the transverse axis of the knee joint).

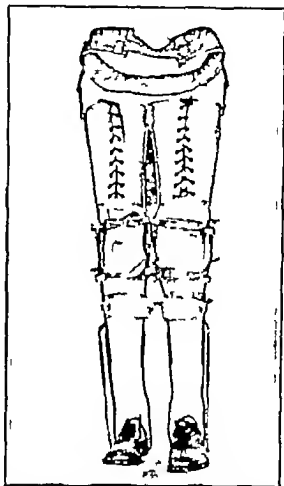


FIGURE 4 Long Leg Brace with Pelvic Band.

Hip joint is a freely movable hinge. Construction of the brace is the same as that in Figure 2.

If the knee joint is placed too high, it will be noted on sitting that the thigh bands are displaced anteriorly and tend to cut into the soft tissues of the posterior surface of the thigh. The reverse is true when the joints are too low. Lower ends of the uprights that are excessively high may tear the patient's clothing when worn under street clothes. There is a tendency, though less marked, for similar pressure to be exerted on the leg with a displaced hinged ankle joint. Care should be exercised in determining the height of thigh bands, since excessive height may cause the formation of decubitus ulcers over the ischial tuberosities and undue pressure on the perineum and genitalia. The superior edge of the band should be parallel to the inguinal

ligament and just low enough to clear those vulnerable structures

### *Long Leg Brace with Pelvic Band (Fig 4)*

The specifications of the long leg brace with pelvic band are as follows

*Long leg braces with uprights of  $\frac{5}{8}$ -by- $\frac{3}{16}$ -inch steel*  
The upright of the pelvic-band attachment is made of  $\frac{5}{8}$ -by- $\frac{3}{16}$ -inch steel, with calf, thigh and pelvic bands of 17-gauge spring steel, padded with  $\frac{3}{16}$ -inch sheet sponge rubber covered with calfskin. The ankle joint is of the caliper type, the knee joint a drop-ring lock-hinge joint, and hip joint a free hinge joint allowing ante flexion and retro flexion at the hip. The drop-foot spring is fixed above and is detachable at the shoe by means of a slotted plate over the button of the instep bar. The pelvic band is secured by a single padded leather strap. The weight of the brace with shoes is 12 pounds, 9 ounces.

*Indications* Analysis of component parts of this brace indicates that the only additional feature, compared with the long leg brace, is the pelvic band. This is attached by an increase in the length of the lateral uprights of the long leg braces and fastening of the band uprights with a freely movable hip joint. No lock is attached. Its adoption for the paraplegic patient is based on specific indications. The level of the injury (Table 1) corresponds roughly to the same level indicating the double upright long leg brace described above. Injuries from the third lumbar segment or cauda equina, or both, that are so complete as to deprive the patient of the functions discussed above under the indications for the long leg brace will in some cases require the pelvic-band extension. The same foot and ankle support is needed, as well as the capacity to maintain the knee in extension in a standing position. The additional factor involved is the loss of part or all of the function of the internal and external rotators of the thigh. The rotation deformities occasioned by the loss of these muscles comprise the chief indication for the pelvic-band extension. The loss of the external thigh rotators with some remaining function of the internal rotators results in a medial rotation deformity of the lower extremities if long leg braces alone are used. This position renders it difficult for the patient during ambulation to swing through smoothly and to regain balance properly. Conversely, unopposed external rotation of the extremities, with resulting external rotation of the feet, interferes even more with these maneuvers. The specific function of the pelvic band is to correct this muscular imbalance by fixing the lower extremities in the proper anteroposterior alignment of 5° external rotation. As would be expected, no appreciable lateral stabilization of the hips can be obtained with the pelvic band, since the chief point

of such instability in high lesions is in the lumbar portion of the spine. It may be possible to determine the need for the addition of a pelvic band only by clinical study of the patient's ability to maintain proper alignment of the lower extremities in ambulation. It is essential that no lock be placed on the hip joint, since the normal hip-joint action must be preserved regardless of the gait used. The hip joint of the brace must be placed at the proper level to obtain maximum function of that joint. Its position should be opposite the superior border of the greater trochanter, which is the point of exit of the transverse axis of the hip joint. When the joint is too high, there is downward traction on the pelvic band, as well as undue pressure on the anterior aspect of the thigh by the thigh band when the patient is in the sitting position. If the joint is placed too low, there is upward thrust on the pelvic band and pressure on the posterior aspect of the thigh. The pelvic band should fall midway between the crest of the ilium and the greater trochanter to avoid pressure over the bony prominences, with possible decubitus-ulcer formation. The comfort of the patient must also be considered with injuries of this level since the sensory level is usually below the point of contact with the band.

### *Long Leg Braces with Back-Brace Attachments (Fig 5 and 6)*

The specifications of these braces are as follows

*Long leg brace and lateral supports of back brace*  
are of steel,  $\frac{5}{8}$  by  $\frac{3}{16}$  inch, with calf and thigh bands of 17-gauge spring steel, a back band of 17-gauge spring steel or duraluminum, padded with a  $\frac{3}{16}$ -inch sponge rubber covered with calfskin. The ankle joint is of the caliper type with detachable drop-foot springs. The knee joint has a drop-ring lock, with a hinge joint, and the hip joint is of the freely movable hinge type, abdominal support is provided by a piece of 11-ounce duck with multiple canvas web straps.

*Indications* This type of brace is limited to the highest levels of injury — that is, generally, those above the third lumbar vertebra (Table 1). Its distinguishing feature is lateral hip stabilization by functional replacement of muscle groups controlling the actions of the pelvis and lumbar spine. The degree of impairment of these muscle groups depends upon the level and completeness of the injury. If muscle analysis indicates deficiency of clinical importance, support must be sought to replace the following vital functions: maintenance of erect posture of the trunk, lateral stability of the pelvis and lumbar spine and maintenance of the normal pelvic inclination. The first of these functions is performed by the iliocostalis lumborum, longissimus dorsi and quadratus lumborum, which are pre-

dominantly innervated by the first four lumbar segments. They also act as lateral flexors by contraction of the homolateral group with the simultaneous relaxation of the contralateral group. Although the intrinsic muscles surrounding the hip joints contribute appreciably to pelvic stability, the lumbosacral group appears clinically more important. The flexors of the pelvis and lumbar spine have a dual function to perform and would be completely lost in a lesion at the level of the sixth thoracic segment or higher. They not only are important as flexors of the lumbar spine but also interact with the extensors of the pelvis and lumbar spine to maintain the normal angle of pelvic inclination. This angle, formed between the true conjugate and the horizontal with the patient in the standing position, is normally 50 to 60°. Loss of these two opposed groups results in lumbar lordosis, with marked in-

creased tension after completing the swing through while lifting his crutches forward to begin the next swing through. The ability to get the hips forward after completion of one swing through in preparation for the next is essential for efficient swing-through ambulation regardless of the type of brace employed.

It is with the use of this brace that the necessity for proper preambulation therapy becomes most evident. Spasm of muscles acting on the thigh, pelvis and trunk must be relieved. Otherwise, the patient will be subject to sudden "jacking" forward or backward as the result of a mass reflex initiated by stretching of these muscles in the act of swinging. The patient must have completed the basic maneuver of balance, since it is particularly important in lesions of this level that this stability and feeling of confidence be acquired. Should all medical therapy of a well developed mass reflex fail and the patient refuse surgical correction, this type of brace cannot be employed, and consequently the most efficient ambulation cannot be attained. The alternative is the long leg brace with pelvic band with hip locks and a wider abdominal support. This combination allows the patient to substitute flexion and

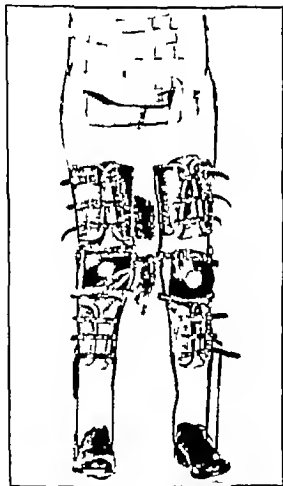


FIGURE 5 Long Leg Brace with Back Attachment (Front View)  
Hip joint is a freely movable hinge. Construction of the brace is the same as that in Figure 2.

crease in the angle of pelvic inclination. This lordosis is quite disabling and virtually prohibits the attainment of balance and subsequent ambulation. The back brace is designed to maintain extension of the trunk by articulation with the thoracic cage above and the lateral long leg supports below. The pelvic extension produced by the inferior transverse portion of the back attachment, together with the replacement of the abdominal musculature function by the abdominal support,<sup>4</sup> tends to maintain the normal pelvic inclination. Side sway at the hips is

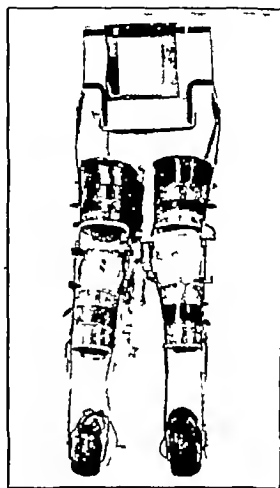


FIGURE 6 Long Leg Brace with Back Attachment (Rear View)

tension after completing the swing through while lifting his crutches forward to begin the next swing through. The ability to get the hips forward after completion of one swing through in preparation for the next is essential for efficient swing-through ambulation regardless of the type of brace employed.

It is with the use of this brace that the necessity for proper preambulation therapy becomes most evident. Spasm of muscles acting on the thigh, pelvis and trunk must be relieved. Otherwise, the patient will be subject to sudden "jacking" forward or backward as the result of a mass reflex initiated by stretching of these muscles in the act of swinging. The patient must have completed the basic maneuver of balance, since it is particularly important in lesions of this level that this stability and feeling of confidence be acquired. Should all medical therapy of a well developed mass reflex fail and the patient refuse surgical correction, this type of brace cannot be employed, and consequently the most efficient ambulation cannot be attained. The alternative is the long leg brace with pelvic band with hip locks and a wider abdominal support. This combination allows the patient to substitute flexion and

extension in the lumbar spine for normal hip motion while splinted by his spastic muscles. This is not efficient ambulation and is never recommended as the procedure of choice, but only as a last resort under these circumstances.

The height of the back brace has been the subject of much discussion and experiment, but the optimum level has proved to be 4 cm. below the inferior angle of the scapulas. This is sufficiently high to allow good articulation with the lower portion of the thoracic cage and yet low enough to permit free action of the scapulas and other elements of the pectoral girdle. Higher back braces are superfluous since the thoracic cage is well supported structurally by ligaments and the pectoral girdle. A positive objection to braces extending above this point is the

ward. Unless a caliper lock is employed in addition to stabilize this ankle joint, some stability may be sacrificed. This is justifiable since it means the difference between a brace that is practicable for use and one that is not.

### Miscellaneous (Fig 7)

In patients whose injuries occur above the first thoracic segment, certain special appliances may be made for the arms, depending upon the degree of brachial-plexus involvement. Among these are the triceps brace to maintain the arms in extension and a leather wristlet to maintain wrist stability. The knee strap is used when necessary to prevent genu varus or valgus, and the "T" strap performs a similar function at the ankle joint. The cock-up splint is made of a wire frame with transverse canvas web supports.<sup>7</sup> The sleeper brace and cock-up splints are used in the earlier stages (I and II) before the patient becomes ambulatory as an aid in preventing flexion contractures of the ankle and knee. The detachable spreader bar is occasionally employed in teaching the swing through in Stage IV, but further use is discouraged, it is attached to the medial uprights at ankle level by means of bolts with wing nuts. The Taylor back brace, not shown, is used for correction in the occasional case in which severe kyphosis develops in high thoracic and cervical injuries.

### DISCUSSION

It will be noted in the foregoing discussion of the four general types of supports that the indications are based primarily on the assumption of a complete lesion at the level indicated. Although such an injury is actually present in the majority of patients, a smaller proportion of incomplete injuries of the cord and cauda equina will be encountered. In such cases it is impossible to state categorically in advance exactly what type of appliance will be indicated, not only because of wide variance in the initial pattern of muscular dysfunction but also because there may be gradual improvement in muscular power over a period of months after the initial trauma. Muscle analysis is indispensable in partial lesions as the initial step when the patient is ready for bracing. With this information at hand and the specific function performed by each type of appliance borne in mind, a rational approach may be made to the specific problem presented. In cervical-cord injuries the extent of the brachial-plexus involvement will determine the appliances necessary for the upper extremities.

Although a detailed study of ambulation is beyond the scope of this communication, it is essential in any discussion of braces at least to mention the type of gait that may reasonably be employed with a given appliance. Patients requiring only drop-foot braces approach most nearly the normal gait. They may use ultimately either one or two canes and walk

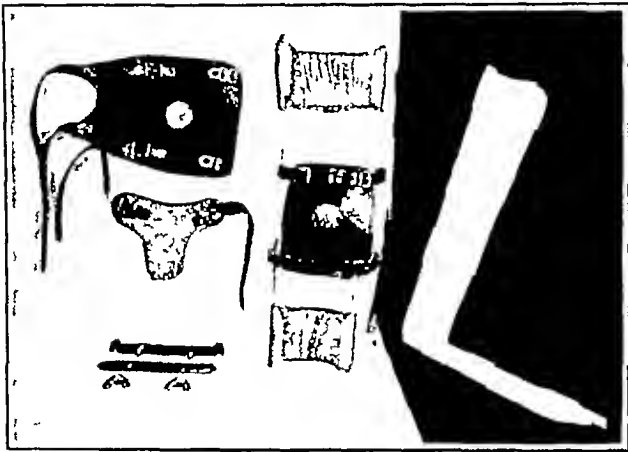


FIGURE 7 Miscellaneous Braces

Upper left, knee strap, middle left, "T" strap, lower left, detachable spreader bar, center, sleeper brace, and right, cock-up splint

interference offered to the proper use of crutches, which become entangled with the back-brace extension. The height has a direct bearing on the total weight, which at best exceeds that of any other type. Attempts to substitute duraluminum for the uprights and transverse struts of the back brace have resulted in failure because of the great stress that the appliance is called on to bear. Some weight may be spared with substitution of sheet duraluminum for the 17-gauge steel in the main body of the back support, but further use of this material is foredoomed to failure.

It was primarily for patients with back braces that the caliper with a detachable drop-foot spring was developed, since the stirrup-type leg brace with shoes and back brace attached requires the assistance of one or two persons in application and removal of the unwieldy device. With calipers and a detachable drop-foot spring the patient can wear shoes continually, insert the calipers into the shoes and then proceed to lace the brace from below up-

almost normally except that they tend to proceed on a rather wide base with steppage gait. Initially, it may be necessary to train such patients with crutches instead of canes, but the use of crutches should be discouraged as rapidly as possible — the obvious objections to crutches are that they call attention to the patient's handicap and promote a feeling of dependency. The type of gait to be employed by patients with long leg braces will depend on the degree of function remaining in the thigh flexors. Should the thigh flexors be adequate to advance the legs even though not strong enough to support the patient's body weight, either the four-point or the more rapid two-point crutch gait is feasible. In either case, he should also be taught the swing through, which is the most rapid of all gaits and may be required in situations in which speed is desirable, as in crossing streets with traffic lights. This type of gait can be taught to any properly prepared patient with a complete or partial lesion below the first thoracic segment and is mandatory for those with loss of thigh flexors and higher lesions (the second lumbar segment upward). The pelvic-band group will not usually exhibit enough function to allow the two-point and four-point gaits and consequently must be taught the swing through with the preliminary temporary swing-to gait. For patients requiring back braces the only practicable gait for distance walking is the swing through, which is taught to all patients except those with lesions above the second thoracic segment that are so severe as to cause gross impairment of arm function. As in the pelvic band group, the swing to is taught as a preliminary to learning the swing through. The swing to is retained only for maneuvering in close quarters where the lack of space renders the swing through impossible. Since the hip joint must be movable for efficient ambulation, it is incumbent on these patients to exercise more skill and balance than lower injuries demand. The patient should not be permitted to attempt a swing to until he has thoroughly mastered the art of balancing with first one and then the other crutch off the floor, unsupported by either an instructor or other artificial means. The poise and sense of confidence gained thereby is basic in the subsequent steps of ambulation progressing through the swing to to an efficient swing through. Lesions high enough to involve the brachial plexus usually force the patient to walk with a swing to or shuffle. This has proved practicable with one of our patients with a complete motor lesion below the fifth cervical segment except for some intact fibers in the seventh and eighth cervical segments. Concurrently and later, all patients must go through a period of intensive mat work and other calisthenics designed to strengthen the pectoral girdle and arms to a point that will permit the stress of weight bearing demanded for ambulation. This is particularly important in the group with higher injuries.

The knee lock used in construction of the long leg braces is recommended after testing of several more complicated types. It is of simple, rugged construction requiring a minimum of machining and repair. The gravity lock is easily placed and fool-proof during use. More elaborate locks are more expensive and prone to damage by twisting or bending.

The width of calf and thigh bands is of practical importance. As a general rule, best results are obtained from narrow bands. Although no difficulties have been encountered, owing to the youth of the patients, circulatory embarrassment may well result in older patients if calf and thigh bands are too wide. This precaution should apply to any patient with venous varicosities, arteriosclerotic changes or other impairment of peripheral circulation.

Steel is the material of choice though its weight is somewhat greater than that of duraluminum. Its durability and capacity to withstand torsion and stress, particularly of the higher braces and in heavy patients, make it irreplaceable by any of the light alloys available. Observations on duraluminum braces constructed here and at other institutions indicate that joints deteriorate rapidly and that twisting necessitates frequent attempts at adjustment, which are rarely, if ever, successful. The calf and thigh bands used on these braces are not of the contour-fitting type advocated by Hessing,<sup>1</sup> since no weight-bearing function is required of them. The considerable time and expense associated with the building of such braces may be avoided.

#### SUMMARY

Preliminary rehabilitation procedures prior to the fitting of braces on patients with spinal-cord injuries are outlined.

Factors involved in choosing the proper brace for patients with spinal-cord injuries, with special reference to the level of injury, are discussed.

Four main types of brace are presented in detail, with the indications for each.

The type of gait to be expected for each level is described.

I am indebted to Mr. Walter Gavin of the Orthopedic Shop, Cushing Veterans Administration Hospital, for his co-operation and assistance.

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# ULCEROGLANDULAR TULAREMIA TREATED WITH STREPTOMYCIN

## A Report of Two Cases

CAPTAIN RAYMOND E. LESSER, M C, A. U. S., AND MAJOR SIDNEY MILLER, M C, A. U. S.

HEILMAN'S<sup>1</sup> demonstration of the effectiveness of streptomycin against *Pasteurella tularensis* in vitro and in vivo has found application in the treatment of tularemia in man. The cases presented below are considered to be of interest because they report additional experience with the use of streptomycin in the treatment of tularemia. Furthermore, they afford an interesting comparison of the effectiveness of treatment of the acute and chronic phases of the disease.

### CASE REPORTS

**CASE 1** A 39-year-old man was hospitalized on February 14, 1947, complaining of "cold sensations," pain in the eyes and back and coughing and sneezing of 2 days' duration.

The past history as obtained at the time of admission was of no related significance except for typhoid fever 29 years previously and malaria in 1930.

Physical examination revealed a haggard but well nourished man who appeared moderately ill. The skin was livid

scratched his right middle finger with a briar, but he had not skinned the rabbits. On the following day a localized area of infection was noted at the site. On the day of admission he experienced chills, fever, headache, general malaise and a tender swelling in the right axilla. He also volunteered the information that "rabbit fever, typhus fever and hemorrhagic fever" were endemic in his home town, Americus, Georgia, the locale of his rabbit hunting. Agglutinations and a culture and smear of the ulcerated area were made, and streptomycin—in a dosage of 3 gm daily—was given. Treatment was continued for 7 days. Within 24 hours the patient experienced dramatic subjective improvement, and in 48 hours the temperature began to regress and the lesion to undergo involution. At the end of 7 days the temperature became normal and remained so for the duration of the hospital stay of 54 days. The local lesion and axillary adenopathy completely subsided 4 weeks after the institution of streptomycin.

The subsequent clinical course was uneventful. The pertinent laboratory data are summarized below, and the clinical course is graphically represented in Figure 1.

On February 14 examination of the blood disclosed a white-cell count of 12,000, with 70 per cent neutrophils, 23 per cent lymphocytes and 7 per cent monocytes. The urine was normal. The blood Kahn test was negative. On February 25 a blood culture was negative, and smear and culture of the ulcer were negative for *Past. tularensis*, agglutinations for the organisms of typhoid, paratyphoid and non-dulant fever, as well as those for salmonella and typhus (proctus x 19), were negative. Agglutinations for *Past. tularensis* were +++++ in a dilution of 1:40, +++ in one of 1:80 and negative in one of 1:160. On March 6 the agglutination was +++++ in a dilution of 1:1280, ++ in one of 1:2560 and negative in one of 1:5120. On March 10 the agglutination was +++++ in a dilution of 1:160 and ++ in one of 1:1280. On March 19 the agglutination was +++++ in a dilution of 1:320, ++ in one of 1:640 and negative in one of 1:1280, and on April 7 it was +++++ in a dilution of 1:160, ++ in one of 1:640 and negative in one of 1:1280.

Three x-ray examinations of the chest during the initial 10-day period were negative.

**CASE 2** A 26-year-old paratrooper was hospitalized on April 24, 1946. He complained of right axillary and right epitrochlear swelling associated with numbness of the fourth and fifth fingers of the right hand of 2 months' duration. During that time he had lost 17 pounds in weight and had observed that the "swellings" had been increasing in size, at the time of admission they had become painful. The patient had been rabbit hunting in January, previous to and at the time of which he had had a "sore" on the ring finger of the right hand. After he dressed the rabbits the "sore" on the right ring finger became deeply infected, and red streak extended to the wrist. Two weeks later he experienced chill and fever. After these symptoms had persisted for 1 week he reported to another Army installation, where he was treated for malaria, the fever persisting for 1 week after hospitalization. On the day of admission he had noted the onset of aching in the muscles and joints.

Physical examination revealed a well developed man, who showed signs of recent weight loss. There were numerous small, nontender shotty lymph nodes in the anterior cervical triangle. In the right axilla there were three tender nodes which were rubbery in consistence and measured 1 or 2 cm in diameter. A similar tender right epitrochlear node was present. When palpated, a linear structure that was considered to be the ulnar nerve moved on manipulation of the node and produced a shocking type of ulnar paresthesia. An ulnar hypesthesia of the fourth and fifth fingers was also present. A circular scar, measuring 5 mm in diameter, was on the medial dorsal surface of the terminal phalanx of the fourth finger of the right hand.

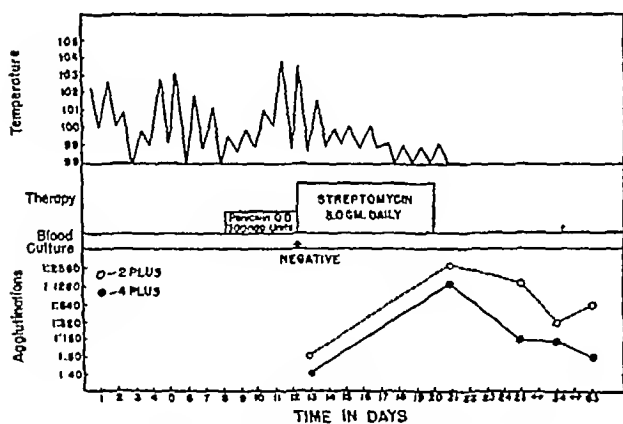


FIGURE 1 Pertinent Laboratory Data and Clinical Course in Case 1

Except for a moderately injected throat and increased breath sounds at the left base, the findings were not remarkable.

On the following day the patient began to manifest a spiking, remittent type of fever. The examining ward officer believed that the patient had a virus pneumonia. When the temperature continued and coarse rales were noted at the left base, previous supportive and symptomatic measures were supplemented by 300,000 units of calcium penicillin in beeswax and peanut oil each day. Despite this therapy the clinical course remained unchanged. Two weeks after admission the examining ward officer first noted an umbilicated, ulcerative lesion with a necrotic center on the dorsal surface of the right middle finger at the distal phalangeal joint, measuring 1.5 cm in diameter. The edges were raised, erythematous and indurated. A single tender, firm lymph node measuring approximately 3 cm in its greatest diameter was palpable in the right axilla. The presumptive diagnosis of tularemia was entertained, and corroborative studies were made.

Further questioning revealed that the patient had been rabbit hunting 3 days before admission. He stated he had

Examination of the blood disclosed a white-cell count of 7500, with 55 per cent neutrophils. A smear was negative for malaria. The urine and the serologic findings were normal. The corrected sedimentation rate was 11 mm. in 1 hour (Wintrobe method). Two agglutinations for *Past. tularensis* were negative. The presumptive diagnosis of tularemia was so strongly held that it was requested that the specimen be sent to the Service Command Laboratory where agglutinations for *Past. tularensis* were reported + + + + in a dilution of 1:320, and + + in one of 1:2560. X-ray examination of the chest was negative.

During the hospital stay the patient was afebrile. With the establishment of the diagnosis of tularemia streptomycin therapy consisting of 0.2 gm. every 4 hours for a total of 4.4 gm over a 4-day period was instituted. During treatment

There was generalized lymph node enlargement, a 1-cm., nontender right axillary node, several pea-sized, tender left axillary nodes, two pea-sized, nontender right epitrochlear nodes, three similar nontender left epitrochlear nodes and bilateral tender inguinal nodes on the left.

The temperature was 97.6°F., the pulse 80 and the blood pressure 110/85.

The patient remained afebrile throughout the hospital stay. Shortly after admission the left epitrochlear and left inguinal lymph nodes were surgically removed. The former was extracted and cultured on cystine blood agar. However, no growth was obtained. The inguinal node was sent to the area pathology laboratory which reported chronic lymphadenitis. X-ray examination of the left hip was negative.

Because of the rise in agglutination titer as well as the significant change in clinical course it was believed that the

TABLE 1 Agglutination Determinations in Case 2

DATE	1:40 dilution	1:80 dilution	1:160 dilution	1:320 dilution	1:640 dilution	1:1280 dilution	1:2560 dilution	1:5120 dilution
4/25/46	Negative							
4/30/46	Negative							
5/6/46	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
5/8/46*	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
5/24/46	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
6/3/46	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
6/19/46	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
6/26/46	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
7/25/46	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
8/8/46	+ + + +	+ + + +	+ + + +	+ + + +	+ +	+ +	+ +	Negative
10/22/46	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	-
1/17/47	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	-
2/24/47	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	-
3/3/47	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	-
3/6/47†	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	Negative
3/11/47	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	-
3/14/47	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	-
3/19/47	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ + + +	-
4/22/47	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ +	+ +	Negative
5/7/47	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ +	+ +	Negative
6/15/47	+ + + +	+ + + +	+ + + +	+ + + +	Negative	+ +	+ +	Negative

\*Streptomycin, in total dosage of 4.4 gm., given between May 11 and 15

†Streptomycin, in total dosage of 12.0 gm., given between March 4 and 11

there was beginning regression of the lymphadenopathy and diminution in the weakness. One week later all tenderness of the lymph nodes had subsided but slight residual adenopathy remained. The patient, who was much improved subjectively, was discharged to duty 35 days after admission.

After discharge he was seen periodically as an outpatient. Objective and subjective improvement continued, with complete resolution of the adenopathy and with ability to carry on with military performance. However, he still complained of some weakness and did not completely regain the weight that he had lost.

Determinations of agglutination for *Past. tularensis* were made monthly and remained constantly + + + + in a dilution of 1:160 during the ensuing months.

Except for weakness and nausea following exertion the patient remained well until December. He experienced a mild aching sensation in the left thigh, left leg and left lower quadrant. When he arose each morning associated malaise returned. The symptoms were of gradual onset but increased severity. On January 6, 1947 he noted for the first time a recurrence of lymphadenopathy in the left epitrochlear region. At the unit dispensary an agglutination for *Past. tularensis* was reported as + + + + in a dilution of 1:1280—a higher titer than at any time previously or subsequently in the illness. On February 3 the aching pain in the left axilla and left leg became severe. The leg pain apparently originated in the left inguinal region and was associated with left inguinal adenopathy; the pains radiated down the leg, were aggravated by exercise and were relatively constant. A novocain injection into the left groin produced relief for 1 hour. Neuropsychiatric examination revealed no psychoneurotic tendencies.

On February 24 the patient was readmitted to the hospital because of the symptoms and clinical course described above. Physical examination revealed a slightly toxic and chronically but not seriously ill patient.

patient was experiencing a relapse. Therefore, on March 4 streptomycin was started consisting of 3 gm. daily for 7 days in divided doses for a total of 21 gm. At the conclusion of therapy the patient felt markedly improved and the adenopathy slowly regressed. Previously, he had lost 15 pounds in weight. One month after the conclusion of therapy he had regained 7 pounds. There was no adenopathy, and the agglutination determination was + + + + in a dilution of 1:160 and + + in one of 1:320. However the last determinations were + + + + and + + in dilutions of 1:160 and 1:640 respectively on May 26. Urinalyses were negative during the period of observation. An electrocardiogram was normal. A bromsulphalein test (5 mg dose) showed no retention of the dye in 1 hour. The corrected sedimentation rate was 9 mm. in 1 hour (Wintrobe method) on two occasions.

The agglutination determinations are presented in Table 1

## DISCUSSION

The effectiveness of streptomycin treatment in the cases reported above parallels that which has appeared in the literature to date.<sup>1-12</sup>

Case 1 afforded no particular problem once the diagnosis had been established. The response was excellent, so far as both morbidity and mortality were concerned, and the effectiveness of streptomycin was again demonstrated. Case 2, however, presented a more complex problem.

Several features present themselves for discussion. The effectiveness of streptomycin when latency exists between initial onset of the disease and the institution of treatment does not seem to be en-



hanced Although the clinical response to streptomycin was definite, the subsequent course of the disease indicates probable inadequacy of dosage initially It may also indicate decreased effectiveness of treatment when a delay occurs between the initial phase of the disease and the institution of therapy The recurrence of symptoms associated with variation in serologic titer of significant degree suggests that criteria for chronicity should be extended farther than the number of days of temperature above 98.6°F, the duration of buboes and the number of days in bed, as suggested by Foshay and Pasternak.<sup>6</sup> Evidence for relapse as manifested by serologic and clinical changes may be correlated with the retention of living bacteria within the recovered patient The inability of streptomycin to effect lasting remission in Case 2 was probably due not only to this fact but also to development of resistance by the organism to the antibiotic agent The initial amount of streptomycin used may be considered inadequate in the light of current knowledge of organism sensitivity It is unfortunate that such studies were not available in this case, in which the course of events suggests the importance of early control of the disease before maximum invasion has occurred

## SUMMARY

Two cases of ulceroglandular tularemia treated with streptomycin are presented in which the course paralleled that which has appeared in the literature to date

The mechanics for failure to effect a lasting cure in one case are discussed

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## THE EFFECT OF SURGICAL OPERATIONS ON THE BROMSULFALEIN-RETENTION TEST\*

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THERE are several reports in the literature dealing with the effect of surgical operations on liver function. The available material was recently reviewed.<sup>1,2</sup> Most workers report changes in a high proportion of patients after surgery under general or spinal anesthesia. The hippuric acid test was used in several cases but has been criticized on theoretical grounds. The principal objection is that it depends on the integrity of kidney function, which may be impaired immediately after a surgical operation. Other authors have reported results obtained with the bromsulfalein-retention test using an injection of 2 mg. of the dye per kilogram of body weight.<sup>2</sup> It has recently been shown that the bromsulfalein-retention test is rendered more sensitive by the use of a dose of 5 mg. per kilogram of body weight.<sup>3</sup> Finally, in view of the report that mechanical trauma to the liver may produce impairment of its function,<sup>4</sup> it seemed worth while to evaluate the effect on the liver of extra-abdominal operation so as to exclude the possible factor of mechanical trauma.

The work reported below represents an attempt to detect changes in the function of the liver following extra-abdominal operations by means of the bromsulfalein-retention test modified so as to make it more sensitive.

In addition to this procedure blood was obtained for thymol-turbidity and cephalin-flocculation tests.

Bromsulfalein retention was determined on non-fasting patients according to the method of Mateer et al.,<sup>3</sup> 5 mg. per kilogram of body weight and a thirty-minute period being used. Readings of bromsulfalein retention were made by comparator block<sup>5</sup> matching.

The cephalin-flocculation test was done by the method of Hanger,<sup>6</sup> using the Difco reagent. A single twenty-four-hour reading of the reaction was recorded.

In the thymol-turbidity test the technic described by MacLagan<sup>6</sup> was used and the values expressed in cubic centimeters of a suspension of barium sulfate as recommended by Ley et al.<sup>7</sup> The reaction of the thymol reagent as measured by the Beckman electrometer was pH 7.8.

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<sup>5</sup>Kindly supplied by Hynson, Westcott and Dunning, Philadelphia. With 5 mg. of dye per kilogram of body weight, a correction factor is used in the readings.

### MATERIAL AND METHOD

A group of 20 patients admitted to the Memorial Hospital for operative treatment was studied. Half the patients (Group I) were on the Head and Neck Service, and the other half (Group II) on the Breast Service. This type of patient was selected to avoid the inclusion of cases in which intra-abdominal procedures had been performed. The possibility of mechanical trauma to the liver was therefore excluded. In each group of 10, the patients were unselected and were studied as they were admitted on the wards.

The state of nutrition of each patient was appraised by means of the history and general appearance, the weight and the detection of clinical signs of nutritional deficiencies. All patients studied were found to be in a satisfactory state of nutrition except 1 (Case 7), who was obese. Clinical evaluation of pre-existing liver damage was done by questioning about the existence of past liver disease, exposure to toxic factors including alcoholism and the detection by physical examination of such signs as enlargement of the liver and spleen, icterus, collateral circulation and spider angiomas. By these criteria, all patients were found to be free of clinically detectable liver disease before and after the operation period except 1 (Case 2), whose liver was slightly enlarged and who had a past history of heavy alcoholic intake.

Two patients, Cases 12 and 14, were found to have high blood pressure on admission. The former had a blood pressure of 170 systolic, 120 diastolic, auricular fibrillation and slight dyspnea on exertion, but no peripheral edema. Functionally she belonged to Group II-C of the classification of the New York Heart Association, her cardiac status was not clinically altered by the operative procedure. The other patient had a blood pressure of 210 systolic, 90 diastolic. Her only cardiac symptom was slight dyspnea on exertion. This case should be considered in Group I-B of the classification of the New York Heart Association, the operation did not alter her cardiac status.

The over-all clinical picture, including the type of operation and its duration, is presented in Table I. Some patients (Cases 1 to 10) received intravenous pentothal sodium as a general anesthetic, in others (Cases 11 to 20) operation was performed under general anesthesia by nitrous oxide, oxygen and ether. Every patient prior to operation received an injection of 15 mg. of morphine, 0.6 mg. of atropin and 100 mg. of nembutal or 100 mg. of luminal.

In each group the patients were classified according to decreasing severity of operation. Thus in Group I, the most serious operation was performed in Case 1, and the least serious in Case 10. In Group II the most serious operation was performed in Case 11, and the least serious in Case 20. Evaluation of the gravity of the surgical procedure is

admittedly arbitrary and was based mainly on two criteria: extent of trauma, with particular emphasis on bone resection, and duration of the procedure. This classification does not pretend to be an absolute one but rather reflects the general trend of severity within each group.

The blood pressure was followed by readings obtained at fifteen-minute intervals during the entire procedure and immediately thereafter. A fall of blood pressure of 20 to 40 for not longer than half an hour was considered a sign of mild shock. A more serious manifestation of shock was not observed. Replacement fluids given in the course of the operation are indicated in Table I. Fever was absent at the time of operation in all patients.

On admission the bromsulfalein-retention test was carried out, and blood was obtained for the thymol-turbidity and cephalin-flocculation tests. This procedure was repeated within an hour of the patient's return from the operating room. In most cases the patient was still under the influence of the anesthetic when the second test was done. At least a one-day interval separated the preoperative and postoperative tests. The patient was tested again once or twice several days later when he was well on the way to recovery.

### RESULTS

#### *Bromsulfalein Clearance*

Before the operation the retention of bromsulfalein in all patients did not exceed 10 per cent, with the exception of 1 patient (Case 7), who had a retention of 12 per cent. The upper limit of normal retention of bromsulfalein after thirty minutes with the technic used is 10 per cent, and all patients studied can therefore be considered as having had a normal test preoperatively.

Immediately after the operation, there was a marked elevation of the amount of bromsulfalein retained in the blood in several patients; the increased retention could be considered significant in Cases 1 to 9, 11, 12, 14, 15 and 16. The elevation was absent or insignificant in the others. The increased retention was pronounced in 6 cases in Group I (Cases 1, 2, 3, 5, 7 and 8), the greatest retention being observed in Case 8, and in 2 patients in Group II (Cases 11 and 12). The increased retention was not maintained, and the test returned toward normal in the following days.

#### *Thymol Turbidity*

The usually accepted upper limit of normal with this test is a turbidity corresponding to 1.75 cc. of barium sulfate suspension. Four of the 20 patients initially had a somewhat elevated test (Cases 1, 11, 14 and 20). There was no general increase after the operation. One patient (Case 7) showed a

significant increase. In the others the thymol turbidity either remained unchanged or decreased.

### *Cephalin Flocculation*

A normal test is represented by absence of flocculation (0) or a + reaction. Five patients (Cases 1, 4, 5, 8 and 10) had an abnormal flocculation test preoperatively. The change in cephalin flocculation postoperatively was not consistent, increasing in some patients and decreasing in others. Most patients in Group II, with the exception of Case 19,

In Group I there was no absolute correlation between the severity of the operation and the amount of dye retained postoperatively. For instance, the patient (Case 8) whose operation was considered less severe than that on the 7 patients preceding her in the classification of Table 1 had the highest degree of retention. In Group II the correlation was better, since the greatest retention of dye was observed in the first patients of the group (Cases 11 and 12). If the two groups of patients are considered together, there seemed to

TABLE 1 *Clinical Data*

CASE No	AGE	SEX	DIAGNOSIS	OPERATION	DURATION OF OPERATION	FALL IN BLOOD PRESSURE	FLUIDS	OTHER DISEASE
	yr				hr		cc	
1	64	M	Squamous cell carcinoma of gingiva	Local excision of tumor and mandible and radical neck dissection	3	0	500 (glucose) 500 (blood)	—
2	57	M	Squamous cell carcinoma of tongue	Glossectomy-radical neck dissection	4	0	500 (glucose) 500 (blood)	—
3	38	M	Metastatic squamous cell carcinoma of neck	Radical neck dissection	3½	Mild	3000 (glucose) 1000 (blood)	—
4	54	F	Carcinoma of salivary gland	Resection of maxilla and antrum	1½	0	0	—
5	34	F	Adenocarcinoma of parotid gland	Removal of parotid gland	2½	0	1000 (glucose) 500 (blood)	—
6	54	M	Adenocarcinoma of parotid gland	Removal of parotid gland	¾	0	0	—
7	54	F	Hashimoto struma	Hemithyroidectomy	1	0	500 (glucose)	—
8	60	F	Thyroglossal cyst	Excision of cyst	1	0	0	Epilepsy
9	72	F	Squamous cell carcinoma of tongue	Partial glossectomy	¾	0	0	—
10	49	M	Previous squamous-cell carcinoma of gingiva, surgical defect	Plastic upper lip, skin graft	1	0	0	—
11	44	F	Carcinoma of breast	Radical mastectomy	2¾	0	500 (glucose)	Anemia (hemoglobin of 60%)
12	58	F	Carcinoma of breast	Radical mastectomy	2¾	Mild	500 (glucose)	Hypertensive heart disease, with failure
13	56	F	Carcinoma of breast	Radical mastectomy	2	Mild	500 (glucose)	—
14	60	F	Intraductal papilloma of breast	Local excision	¾	0	0	Hypertensive heart disease, with failure
15	38	F	Periductal mastitis	Local excision	¾	0	0	—
16	32	F	Fibroadenoma of breast	Local excision	¾	0	0	—
17	32	F	Unilateral mastitis	Local excision	½	0	0	—
18	48	F	Duct papilloma of breast	Local excision	¾	0	0	—
19	47	F	Fibroadenoma of breast	Local excision	½	0	0	—
20	30	F	Sclerosing adenosis of breast	Local excision	¾	0	0	—

had a normal cephalin flocculation initially, which remained normal postoperatively.

### DISCUSSION

The data show that in 14 of the 20 patients there was a significant increase in the retention of bromsulfalein postoperatively as compared to the amount retained before the operation. The retention of dye was very pronounced in several cases. Whereas all patients, with the possible exception of 1 (Case 7), initially had a normal clearance, the increased retention following the operation in 14 cases resulted in postoperative values that were considered abnormal and indicative of liver dysfunction.

be a correlation between severity of operation and retention of dye, since the last patients of Group II, who probably underwent the least severe type of surgical procedure, also showed the smallest degree of retention postoperatively.

It is obvious that the criteria by which the severity of the operations was evaluated are not absolute, and other factors than the ones considered above may have played a role.

The mechanism by which a surgical operation produces such marked changes in bromsulfalein retention is not entirely clear. Liver dysfunction is a conspicuous and early sign of shock.<sup>8</sup> The early stages of shock may not be manifested by a fall of blood pressure at a time when anoxemia of internal

organs such as the liver and the kidney has already taken place.<sup>9</sup> It is therefore conceivable that although the patients in this series either did not experience a fall in blood pressure or at most showed a slight and transitory fall, they had a certain degree of anoxemia of the liver during the operation, explaining the reduced ability of this organ to clear the blood of dye. In that case, the increased retention of bromsulfalein following an operation might be significant as a measure of the amount of injury inflicted on internal organs by a surgical procedure.

If the changes in bromsulfalein retention observed denoted liver dysfunction, the abnormality appeared to be reversible and did not persist longer than a few days. Normal or nearly normal values were observed in almost all patients a few days after the operation.

So far as the thymol turbidity and cephalin flocculation were concerned, it was not expected that the tests would show any significant change. These procedures depend entirely on the presence of an abnormal globulin constituent in blood plasma, and

TABLE 1 (Continued)

CASE NO.	BROMSULFALEIN RETENTION				THYMOL TURBIDITY				CEPHEALIN FLOCCULATION			
	PRE-OPERATIVE %	IMMEDIATELY POST-OPERATIVE %	POST-OPERATIVE* %	POST-OPERATIVE* %	PRE-OPERATIVE	IMMEDIATELY POST-OPERATIVE	POST-OPERATIVE	POST-OPERATIVE	PRE-OPERATIVE	IMMEDIATELY POST-OPERATIVE	POST-OPERATIVE	POST-OPERATIVE
1	10	40	18 (5)	—	2.0	1.5	0.5	—	++++	+++	++	—
2	4	36	8 (5)	—	1.05	1.25	1.0	—	+	+++	+	—
3	4	40	6 (4)	—	0.7	0.6	0.5	—	0	++	0	—
4	10	22	14 (10)	—	0.5	0.5	0.7	—	++	0	+	—
5	6	32	8 (4)	—	1.7	1.5	1.1	—	++++	++	0	—
6	6	16	18 (1)	12 (3)	0.8	1.0	1.0	0.8	0	+++	++++	+++
7	12	32	32 (1)	14 (4)	1.3	2.1	2.0	1.1	0	+++	+	—
8	0	64	32 (3)	—	0.9	1.2	1.10	—	+++	+	0	—
9	6	14	4 (14)	—	0.7	0.6	0.5	—	0	++	0	—
10	4	6	2 (4)	—	1.1	1.0	1.1	—	++++	+++	++	—
11	10	24	—	—	2.4	0.8	—	—	0	0	—	—
12	6	40	16 (3)	—	1.0	1.3	1.4	—	0	0	0	—
13	4	4	4 (4)	—	0.9	0.9	0.8	—	0	0	++	—
14	6	12	8 (6)	—	2.2	1.2	1.3	—	0	0	0	—
15	8	16	8 (7)	—	0.7	0.6	0.3	—	0	0	0	—
16	6	16	6 (7)	—	1.3	1.0	0.3	—	0	0	0	—
17	4	6	6 (9)	—	1.1	1.3	1.5	—	0	0	0	—
18	8	10	6 (8)	—	0.2	0.4	0.6	—	0	0	0	—
19	4	4	6 (8)	—	1.6	1.6	1.3	—	+	++	+++	—
20	4	6	4 (6)	—	2.1	1.5	1.6	—	0	0	0	—

\*Numbers in parentheses refer to days after operation.

applied to a distant anatomic region. A direct mechanical trauma to the liver during the operation, as in the course of an intra-abdominal operation, seems to be ruled out in the patients of this series by the type of subjects selected.

The anesthesia may have been a contributory factor, although pentothal and ether are not considered to be liver poisons. Nevertheless, this factor cannot be entirely ruled out. The extent of the surgical procedure and its duration, regardless of the type of anesthesia, appeared to be more important. The data do not indicate that the age of the patients was a decisive factor in the production of postoperative liver dysfunction as shown by the retention of bromsulfalein in the blood.

this could hardly be expected to occur during the relatively short duration of the operation. The absence of definite changes in the two tests during the postoperative period indicates that the liver dysfunction detected by the bromsulfalein test in the series of patients studied was not pronounced, and confirms its transitory nature.

These results largely confirm those obtained by previous workers and indicate definite impairment of liver function after protracted surgical operations, even when the operative site is such that mechanical trauma to the liver is ruled out.

The changes in liver function are probably significant in that they may represent one of the factors contributing to the complex syndrome called "post-

operative disease." The prevention and control of these changes deserve further study

### SUMMARY

There was a significant increase in the retention of bromsulfalein immediately after an extra-abdominal operation in 14 of 20 patients studied. No similar changes were observed in the thymol-turbidity and cephalin-flocculation tests.

There was a certain degree of correlation between the severity of the operation and the postoperative appearance of an impaired ability of the liver to clear the blood of bromsulfalein. Other factors, such as anesthesia by ether or pentothal sodium and the age of the patients, appeared less important. The significance of these facts in relation to the physiologic changes brought about by a surgical operation is discussed.

We are indebted to Dr. Hayes Martin and Dr. Frank E. Adair for permission to study their patients.

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## THE PROBLEM OF SULFONAMIDE-RESISTANT HEMOLYTIC STREPTOCOCCI\*

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PREVIOUS reports have discussed the problem and circumstances of the development of sulfadiazine-resistant hemolytic streptococci in the armed forces of the United States during 1944.<sup>1-8</sup> In a civilian community the occurrence of infections due to sulfonamide-resistant hemolytic streptococci<sup>9</sup> indicates that these organisms have had a wide distribution throughout the general population via military personnel. The possibility that these resistant organisms might become an epidemiologic and therapeutic problem in civilian life cannot be dismissed on the basis of the available information. Also, the likelihood of such a situation arising in the general population—that is, the development of sulfonamide-resistant or penicillin-resistant strains of hemolytic streptococci under the common therapeutic and prophylactic regimens—should be considered, and efforts directed toward its prevention.

A study of the sulfonamide sensitivity of hemolytic streptococci in the general population would indicate the prevalence of known sulfonamide-resistant strains and also whether there are naturally resistant strains that might assume increased resistance under proper circumstances. It is the purpose of this paper to present the results of sulfonamide-

sensitivity determinations of hemolytic streptococci as they occurred in a New England population, as well as an analysis of the available information pertaining to the conditions under which sulfonamide-resistant hemolytic streptococci developed.

### METHODS

The cultures studied were obtained from patients admitted to the Evans Memorial and Haynes Memorial Hospitals, serving Boston and the suburban areas surrounding it, during the fall and winter of 1946-1947. These patients were admitted to the hospital because they had clinical evidence of a streptococcal infection or were admitted for observation or study and found to harbor hemolytic streptococci. Most of the strains of hemolytic streptococci were isolated from the nasopharynx of patients who had clinical scarlet fever, others were obtained from streptococcal carriers or patients with pharyngitis, otitis media, pneumonia or wound infections due to the hemolytic streptococcus.

Cultures were obtained by swabbing of the nasopharynx or infected areas with culture swabs. The swabs were wiped on 2 per cent blood-agar plates, streaked and incubated aerobically at 37°C for twenty-four hours. Single colonies of beta-hemolytic streptococci were picked and transferred to blood-agar plates or to broth for further identification and study. The hemolytic streptococci isolated were grouped and typed by the precipitin technique,<sup>10</sup> antiserums for Types 1 to 47 were available. The

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sulfonamide sensitivity was determined by the method of Wilson,<sup>11</sup> horse serum being used, susceptible and resistant strains were always run as controls. Only organisms growing in a concentration of 5 mg per 100 cc of sodium sulfadiazine were considered to be resistant. Occasionally scant growth appeared in the tube containing a concentration of 1 mg per 100 cc; however, owing to the conditions of this test, growth in this tube was not considered evidence of resistance.<sup>11, 12</sup>

### RESULTS

One hundred and sixty-seven Group A hemolytic streptococcus strains isolated during the fall and winter of 1946-1947 were tested for sensitivity to the action of sulfadiazine. The type distribution and sulfonamide sensitivity are indicated in Table 1. Types 18, 30 and 31 were the most prevalent, however, there was no predominant epidemic-type strain prevalent in this area. Types 1, 17 and 19, which were the predominant types in the Navy,<sup>1, 2</sup> did not assume any epidemic prominence in this study.

Of 167 strains of Group A hemolytic streptococci tested for sensitivity to the action of sulfadiazine, 166 were sensitive to its action—that is, none grew in a concentration of sodium sulfadiazine as great as 5 mg per 100 cc. One strain, a Group A, Type 19 hemolytic streptococcus, was resistant to the action of sodium sulfadiazine in a concentration of 25 mg per 100 cc. This sulfonamide-resistant strain was isolated from a patient who had clinical scarlet fever and later developed electrocardiographic and clinical evidence of rheumatic heart disease. This strain was sensitive to 0.0078 units of penicillin, as determined by the method of Rammelkamp.<sup>13</sup>

### DISCUSSION

Recent publications have offered some suggestions regarding the possible origin of sulfonamide-resistant streptococci.<sup>3, 4, 9, 12, 14, 15</sup> From theoretical points of view these resistant bacteria could exist as naturally occurring variants, they could arise as variants of normally susceptible strains as a result of contact with and adaptation to the drug, or they could arise as spontaneous genetic mutants. Whatever the explanation of this phenomenon, once sulfonamide-resistant variants appear they increase in prevalence in a sulfonamide-containing environment as a result of their greater fitness to survive. It is of interest to determine what light recent clinical and epidemiologic experience has shed on this problem.

Although methods to detect the development of sulfonamide resistance by other bacteria in vitro were known, attempts to demonstrate the resistance of hemolytic streptococci to sulfonamides, by the use of ordinary mediums containing sulfonamide inhibitors, were uniformly unsuccessful.<sup>3</sup> The need for a method of demonstrating sulfonamide re-

sistance in vitro became urgent with the failure of the mass chemoprophylaxis program in the armed forces in 1944. During that year Wilson<sup>11</sup> developed a technic that enabled one to determine the ability of hemolytic streptococci to grow in a semisolid medium free of sulfonamide inhibitor and containing respectively 0, 1, 5, 25 and 125 mg per 100 cc of sodium sulfadiazine. This test conclusively demonstrated the presence of sulfonamide-resistant strains of hemolytic streptococci, which were the cause of increasing numbers of upper respiratory infections while sulfonamide prophylaxis was being carried out in the armed forces.<sup>2, 4</sup>

After the first demonstration of sulfonamide-resistant Types 3, 17 and 19 Group A hemolytic streptococci during a program of mass chemopro-

TABLE 1 Type Distribution and Sulfadiazine Resistance of Group A Hemolytic Streptococci

SEROLOGIC TYPE	NO. OF STRAINS	NO. OF SULFADIAZINE RESISTANT STRAINS
3	1	0
5	1	0
6	1	0
17	1	0
17	4	0
18	6	0
19	1	1*
25	1	0
26	1	0
26	4	0
28	5	0
30	6	0
31	6	0
31	6	0
38	3	0
39	1	0
42	1	0
43	1	0
47	1	0
†	117	0

\*This strain was resistant to the action of sodium sulfadiazine in a concentration of 25 mg. per 100 cc.

†Strains not classified by the precipitin method with available diagnostic serum.

phylaxis in the armed forces,<sup>2, 4</sup> it became essential to know if there were any resistant strains before this program was inaugurated in the Navy in December, 1943.<sup>1, 2</sup> This information could be obtained only by tests of cultures that had been preserved prior to this program of mass chemoprophylaxis. No sulfonamide resistance was demonstrated in over 100 of the strains of hemolytic streptococci preserved at the Rockefeller Institute Hospital prior to 1937.<sup>19</sup> Siegel<sup>17</sup> showed that 90 strains of Group A hemolytic streptococci isolated from scarlet-fever patients before 1938 were sensitive to the action of sulfadiazine. Sensitivity determinations on strains of hemolytic streptococci isolated from patients with scarlet fever<sup>12</sup> in the United States Navy prior to December, 1943, did not show any evidence of resistance. Most of these strains were Type 19, and some were isolated from patients who had been receiving small doses of sulfadiazine during a scarlet-fever epidemic in New York City.<sup>19</sup> It should be noted that strains of Type 19 later

appearing in the armed forces were resistant to sulfonamides. From this information it seems safe to conclude that before the program of mass sulfadiazine prophylaxis had been initiated in the armed forces in 1943 there were no known sulfonamide-resistant Group A hemolytic streptococci.

Rantz et al,<sup>14</sup> however, reported the results of testing strains of Group A hemolytic streptococci isolated in the Army from December, 1943, to April, 1944, and observed that some of the typed strains were more resistant than others—that is, that they grew in suspensions of 1 mg and 5 mg of sodium sulfadiazine per 100 cc. The authors were of the opinion that these strains were naturally resistant to moderate amounts of sulfadiazine and were the precursors of the more highly resistant strains such as Types 3 and 17, which later became established as epidemic, resistant strains. The possibility of transfer of these resistant strains to Army personnel by members of the Navy on chemoprophylaxis cannot be ruled out.

Several studies of streptococcal carriers treated with sulfadiazine to rid them of the carrier state are enlightening in demonstrating the possibility of the development of resistance under those conditions of treatment. Strains of hemolytic streptococci isolated from 40 patients before and after treatment with therapeutic doses of sulfadiazine did not show any evidence of the development of resistance to sulfadiazine.<sup>12</sup> Another study of 10 carriers treated with 1 gm of sulfadiazine daily for a ten-week period did not reveal any increase in sulfadiazine resistance of the post-treatment cultures as compared with the pretreatment strains.<sup>17</sup> Hamburger et al<sup>19</sup> treated 45 carriers of Group A hemolytic streptococci with 1 gm of sulfadiazine daily for four-day to fifty-day periods, with no development of sulfadiazine-resistant strains during the treatment period. So far as is known at present, no evidence of the development of resistant strains of hemolytic streptococci has been reported from any rheumatic fever patients who are receiving daily prophylactic treatment with sulfonamides.<sup>20</sup> Under the conditions of the studies cited above, no resistant strains of hemolytic streptococci developed.

The spread and epidemiologic problems that these resistant organisms presented in the armed forces have been summarized in previous reports<sup>3-8, 16</sup>. Although it was known that the civilian population was exposed to these resistant strains of hemolytic streptococci, no epidemics therefrom were reported until 1946, when an outbreak of Type 19 infections appeared in Cooperstown, New York.<sup>9</sup> Except for the Type 19 strains, resistant to 25 mg per 100 cc of sodium sulfadiazine, isolated during that study, none of the types showed any evidence of resistance. In the present report all strains, except the one resistant Type 19 strain, were susceptible to the action of sodium sulfadiazine. Apparently, there have been no problems of therapy in these resistant

streptococcal infections since they can be adequately treated with penicillin.<sup>21</sup>

The results of the present study of 167 strains of Group A hemolytic streptococci indicate that only one strain, which belonged to Type 19, was resistant to the action of sulfadiazine. This strain grew in a concentration of 25 mg of sodium sulfadiazine per 100 cc—the same concentration as the epidemic Type 19 strains that were prevalent in the armed forces. The source of this strain is not known, but it was probably introduced into this area by Army or Navy personnel. The possibility that this resistant strain is a naturally resistant variant cannot be ruled out, but the available information indicates that the resistant organism encountered in this study was the same as that in the armed forces.

The data of this study show that sulfonamide-resistant variants of Group A hemolytic streptococci did not arise in this area of Boston and its environs, where sulfonamides are used in the customary manner in the treatment of patients and where sulfonamide prophylaxis has not been widely employed.

From the accumulated evidence presented, it seems that conditions of mass sulfadiazine prophylaxis as they existed in the armed forces<sup>1, 2</sup> were conducive to the development of sulfadiazine-resistant strains of hemolytic streptococci. Regarding the conditions under which drug-resistant organisms can be expected to arise, one observer has postulated that “the infection shall be a common type providing very large numbers of micro-organisms within which a rare mutation has a chance to arise, and second—and this is the medically important point—that a large proportion of the potential hosts shall be treated with the drug in question.”<sup>16</sup> To date these resistant strains have not presented any particular problem in civilian life and can be adequately treated by penicillin therapy. The possibility of the development of resistant strains of bacteria during large-scale mass prophylactic programs should be kept in mind, and such programs should be used only as an emergency measure.

## SUMMARY

Sulfonamide sensitivity determinations on 167 strains of Group A hemolytic streptococci, isolated from patients from Boston and surrounding suburbs, are presented. Only one strain, Type 19, was resistant to 25 mg per 100 cc of sodium sulfadiazine.

The pertinent literature regarding the development of sulfonamide-resistant hemolytic streptococci is reviewed.

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## MEDICAL PROGRESS

### THE ROLE OF PLEUROPNEUMONIA-LIKE ORGANISMS IN GENITOURINARY AND JOINT DISEASES (Concluded)\*

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THE high incidence of acute joint disease in male patients with positive prostatic cultures, in addition to the knowledge that animals infected with L organisms frequently have arthritis, suggests that pleuropneumonia-like organisms play a role in producing the joint disease in the patients. The hypothesis that this organism is the cause of the arthritis is somewhat supported by the fact that in 2 cases of Reiter's syndrome (as Case II) L organisms were cultured from the knee-joint fluid. However, no L organisms were found in the synovial fluids in the other 11 cases in this series in which a search for these organisms was made.

In women, a relation between the presence of the L organism in the genital tract and the development of joint disease was not so apparent. Among 58 women yielding positive cultures in the original series, only 9 had joint complaints. One of these patients also had gonococci in the cervical cultures. Two other cases were arbitrarily introduced into the series since they had rheumatoid arthritis and formed part of a group of 12 female patients with

rheumatoid arthritis in whom routine examination of cervical cultures for L organisms was made. Five of the 6 remaining patients had had swelling and pain of long duration in various joints. The other patient (Case 10) had an acute arthritis that had developed two weeks after marriage. Her husband (Case 9) also developed joint symptoms eight weeks after marriage, and L organisms were found in the prostate at that time. In view of the high incidence of L organisms in the female genital tract (26 per cent) and the relatively low percentage of joint disease in female patients with positive cultures, there is no definite evidence of a relation between the L organism and the joint disease in these cases. However, the observations in the married couple suggest not only that the joint involvement was related to the L organism but also that certain strains have a greater tendency than others to produce joint disease. Further suggestion of a possible relation between the L organism and joint disease in women was furnished by 2 other patients, seen since the original series was completed, who had acute arthritis at the time cervical cultures were positive for L organisms and negative for gonococci.

Until further information is available concerning the pathogenicity of the various human strains of pleuropneumonia-like organisms, it is difficult to conclude whether or not the conditions produced by these organisms are contagious. Certain findings suggest that they are. The wives of 5 of the men from whose prostates L organisms were cultured

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were studied, and in 2 cases *L* organisms were found in the cervical cultures. In 1 case—that of the married couple discussed above—both husband and wife developed acute arthritis soon after marriage. Beveridge, Campbell and Lind<sup>9</sup> cultured pleuropneumonia-like organisms from 3 of 11 women from whom men had contracted nonspecific urethritis. The fact that the genitourinary, joint or eye symptoms in at least 7 of the men with positive cultures in the present series developed within a few days after sexual exposure suggests that the disease is venereal in some cases. However, in many cases no history of exposure was obtained. The possibility that the gastrointestinal tract was the portal of entry in some cases is suggested by the fact that at least 6 patients had diarrhea just before or at the onset of the disease.

The treatment of diseases produced by pleuropneumonia-like organisms is still in an experimental stage. In rats and mice these diseases have been shown to be prevented or effectively treated in a high percentage of cases by gold compounds<sup>22, 23</sup> and by streptomycin.<sup>24</sup> Penicillin has not been effective in animals.<sup>25</sup> Pleuropneumonia-like organisms are not sensitive *in vitro* to sulfonamides or penicillin, but the growth of some strains has been found to be inhibited by streptomycin in a concentration of 20 microgm per cubic centimeter.<sup>17</sup> In the present series gold was used in only 1 patient (Case 4) and was ineffective. None of the patients treated with sulfonamides or penicillin showed any improvement in the genitourinary or joint symptoms. Streptomycin was used in 8 patients in whom the infection was limited to the genitourinary tract (see Cases 4 and 5), including 4 cases of cystitis, in 1 patient with acute arthritis associated with urethritis, and in 5 patients with Reiter's syndrome (Case 12).<sup>\*</sup> In 7 of the 8 cases of genitourinary-tract infection there was rapid disappearance of symptoms during treatment, and cultures became negative for *L* organisms. The eighth case, in a patient who had had urethritis for sixteen years (Case 4), showed only a transient improvement in symptoms, and the pleuropneumonia-like organisms did not disappear from the urethral cultures. In the patients with acute arthritis or Reiter's syndrome, there was improvement in symptoms during and immediately after treatment. However, evidence of joint inflammation persisted for weeks, and the sedimentation rates remained elevated. In none of the cases were *L* organisms cultured after treatment. Streptomycin therapy did not prevent recurrences of the disease in Case 12. The results of streptomycin therapy were not conclusive but indicate that the drug is probably effective in most cases of uncomplicated genitourinary-tract disease due to pleuropneumonia-like organisms. In Reiter's

syndrome the results were sufficiently suggestive to warrant further trial of this therapy.

### CASE REPORTS

The following brief abstracts include characteristic cases from the various groups.

**CASE 1 (M G H 22349) †** A 33-year-old female research worker who handled rats almost daily and who gave no history of previous genitourinary disease noted sudden onset of tenderness and swelling of the right labium majus 10 days after marriage. On examination an abscess of Bartholin's gland was found. Cervical smears were negative for gonococci. Excision of the abscess *in toto* was performed, and cultures were made at the operating table from the center of the abscess, which contained creamy-yellow pus. These cultures yielded an abundant growth of *L* organisms in pure culture. Streptobacilli or gonococci could not be demonstrated by smear or culture. The patient recovered uneventfully.

**CASE 2** An 18-year-old single girl noted the onset of profuse vaginal discharge 4 days after intercourse. On examination there was an acute vaginitis, with a fiery-red mucosa and yellow purulent exudate. Cultures of this exudate yielded a pure growth of *L* organisms. Gonococci could not be demonstrated by smear or culture. The vaginitis cleared up within 1 week.

### Patients with Urethritis and Prostatitis

**CASE 3** A young married man, 36 hours after extramarital exposure, observed slight urethral discharge. On examination no discharge was apparent, but the prostate was found to be swollen and painful. In the culture made from a sample of urine immediately after prostatic massage many *L* colonies but no gonococci were seen. A second culture 10 days later was negative for *L* organisms and for gonococci. The subsequent clinical course is not known.<sup>‡</sup>

**CASE 4 (M G H 492207)** A 35-year-old married man was admitted to the hospital because of persistent urethral discharge. Sixteen years previously, 3 days after intercourse, he had developed a yellowish urethral discharge and in ginal lymphadenopathy. The discharge had not changed throughout the 16 years despite many types of treatment, including sulfonamides, penicillin and numerous kinds of local therapy. Cultures had always been negative for gonococci, but during the year before admission had been positive for pleuropneumonia-like organisms on several occasions. Examination was negative except for slight urethral discharge and enlargement of the prostate. The patient was treated with streptomycin, in a dosage of 4 gm a day, for 1 week. The discharge disappeared after 1 day of treatment, but cultures of the prostatic secretion continued to show many colonies of *L* organisms. Ten days after treatment was stopped the discharge returned and has persisted for the past 11 months. During this interval he has been treated with myocresine, receiving 325 mg in 5 weeks without effect.

### Patients with Cystitis

**CASE 5 (M G H 532255) §** A 26-year-old single man was admitted to the hospital because of frequency of urination and terminal hematuria. Three years before admission he had had urethral discharge and frequency of urination lasting for several weeks. Subsequently, there had been repeated recurrences of burning and frequency. Two weeks before admission he had first noted blood in the terminal portion of the urine. Cultures had always been negative for gonococci. Examination was negative except for the fact that the prostate was rather soft. The urine was loaded

\*We are indebted to the Committee on Chemotherapeutics of the National Research Council for the streptomycin used during most of this study and to Merck and Company for the streptomycin now being employed for test of its efficacy in the treatment of infections due to pleuropneumonia-like organisms.

†We are indebted to Dr. L. Parsons, of the Massachusetts General Hospital for permission to report this case. Reference to this patient has been made by Dienes and Edsall.<sup>12</sup>

‡This was a patient of the late Dr. Richard F. O'Neil.

§We are indebted to Dr. Fletcher H. Colby, of the Massachusetts General Hospital, for permission to include this case which has also been reported by Kane and Foley.<sup>11</sup>

with erythrocytes and leukocytes. Three routine cultures of urine showed no growth, but cultures on hotted blood ascitic agar contained numerous colonies of pleuropneumonia-like organisms. The patient was given 2 gm of streptomycin daily for 4 days and 1 gm daily for the following 5 days. Cultures became negative for L organisms after 3 days of treatment, and the urinary sediment showed only rare cells. There has been no recurrence of symptoms in the subsequent 14 months.

### *Patients with Chronic Arthritis*

**CASE 6 (M. G. H. 534532).** A 32-year-old married man was admitted to the hospital because of severe pain and redness of the right eye of 1 week's duration. Seven years before admission he had had a urethral discharge, smears from which were reported to contain gonococci. Five years later he had begun to notice migratory pains in the hips, right knee, neck and lower back. Six months before admission the right knee became swollen and painful. Examination showed an iritis of the right eye with marked ciliary injection, an effusion in the right knee and slight tenderness and induration of the prostate. Prostatic cultures showed a moderate growth of L organisms and of non-hemolytic streptococci. The arthritis subsided in 3 months but the iritis still persists at the end of 11 months. During this period central chorioiditis has developed and has been treated with fever induced by intravenous injection of typhoid vaccine. Prostatic cultures have remained positive for L organisms.

It is impossible to determine whether or not the various features of this patient's disease are interrelated in any way.

### *Patients with Acute Arthritis without Eye Involvement*

**CASE 7 (M. G. H. 352561).** A 47-year-old married man noted burning on urination 2 or 3 days after sexual exposure. One week later he developed stiffness of the knees, right wrist and right shoulder. The stiffness of the knees persisted, and 3 weeks later the left wrist became very swollen, red, hot and tender. These symptoms subsided in 2 or 3 days but the right wrist became involved. Examination on the following day showed tenderness, increased heat and pitting edema of the right wrist and the dorsum of the right hand and a moderate-sized effusion in the left knee, which was warm and tender. The prostate was tender and boggy. Culture of the prostatic secretion showed numerous colonies of L organisms and *Staphylococcus aureus*; but was negative for gonococci. All symptoms subsided in 2 weeks though the sedimentation rate remained elevated. There was no recurrence of symptoms during the subsequent 2 years.

**CASE 8 (M. G. H. 315068).** A 29-year-old single man had had a urethral discharge 6 months before admission. Soon thereafter he had noted pain and swelling of the left knee, left third toe and right third finger. There had been no response to sulfonamide therapy but the symptoms subsided slowly over the course of 4 months. Two weeks before admission the urethral discharge recurred and pain developed in the right hip, left shoulder and tarsometatarsal joints on both sides. The patient had had a urethritis said to be of gonococcal origin, 8 years before admission. On examination at the time of admission the left knee contained a moderate-sized effusion and was tender. The prostate was large and boggy. Cultures of prostatic secretion showed abundant L colonies but no gonococci. The patient was again treated with sulfonamides with no effect. The symptoms gradually disappeared over the course of 2 months. Cultures of prostatic secretion were negative for L organisms 4 years later.

**CASE 9 (M. G. H. 291517).** This 38-year-old man the husband of the patient in Case 10, was seen in 1942 when he had been married 8 weeks. He had had urethritis in 1929 and again in 1934. Gonococci were said to have been seen in smears during both these attacks, but they could never be demonstrated at any time thereafter. In 1937, 1940 and 1941 he had been treated for chronic prostatitis, smears showing pus cells but no gonococci. In March 1942, the patient was admitted to the hospital for painful swelling of the left wrist of 3 days' duration. On examination the prostate did not feel abnormal but massage yielded fluid containing 20 to

30 pus cells per high power field. Cultures yielded no gonococci but gave an abundant growth of L organisms, streptococci and diphtheroids. Four months later pain and swelling developed in the right elbow, persisting for 9 months. During this episode the prostate was found to be boggy and the vesicles were tender. Prostatic cultures yielded occasional L organisms and an abundant growth of hacteroides, nonhemolytic streptococci and *Staph. albus*. Four years later the patient had recurrent attacks of pain in the left flank and x-ray study showed a stone in the lower end of the left ureter. At the time of admission for removal of the stone the urine was cultured but showed no growth of pleuropneumonia-like or other organisms.

**CASE 10 (M. G. H. 348216).** A 30-year-old woman, the wife of the patient in Case 9, was admitted to the hospital in March, 1942, 3 days after her husband's first admission. She gave no history of genitourinary disease and had been well until 6 weeks before entry, when 2 weeks after marriage she developed stiff, swollen knees. There was no redness or heat about the knees and the swelling caused only moderate discomfort. No other joints were involved and there was no fever and no constitutional symptoms. Pelvic examination revealed a slight cervical discharge, cultures of which yielded a pure growth of L organisms. No organisms were found in gram stained or Giemsa stained films of the joint fluid and none could be recovered in culture. The patient was discharged unimproved after 1 week. The involvement of the knees gradually subsided during the following year.

### *Patients with Acute Arthritis with Eye Involvement (Reiter's Syndrome)*

**CASE 11 (M. G. H. 440804)\*.** A 26-year-old single man developed a purulent urethral discharge 36 hours after sexual exposure. He was treated with sulfathiazole and sulfadiazine, but the discharge persisted and 3 weeks after onset he noted burning, frequency, urgency and terminal hematuria. Approximately 5 weeks later bilateral conjunctivitis appeared and within a few days he complained of pain in the lumbosacral region, as well as pain and swelling of the right ankle, right shoulder, left elbow and left knee. On examination 3 days later, the temperature was 100.4 F. with slight conjunctival injection and swelling and tenderness of the right ankle, left knee and right sternoclavicular joint. The urethral discharge had subsided but a catheterized specimen of urine was loaded with white cells. Cultures of the urine and prostatic secretion showed an abundant growth of L organisms and a few colonies of staphylococci but were negative for gonococci. Two colonies of L organisms were found in the culture of fluid from the left knee. At the time of discharge, cultures of the urine showed only a few L organisms. The patient was treated with 120,000 units of penicillin without effect but all symptoms subsided slowly during the course of 2 months.

**CASE 12 (M. G. H. 255127).** A 26-year-old single man had had pain in the right ankle and right knee and slight urethral discharge for 2½ weeks before admission. Examination revealed marked swelling of the right knee with an effusion and moderate swelling of the right ankle. The prostate was slightly enlarged and boggy. Three weeks later an iritis developed in the left eye. Culture of the prostatic secretion showed abundant growth of L organisms and many streptococci and colon bacilli but was negative for gonococci. The patient was treated with sulfathiazole and penicillin without effect. The symptoms gradually subsided during the course of 6 months. He had had a similar attack 4 years previously with bilateral conjunctivitis and keratitis, purulent urethral discharge and arthritis. There had been a second attack 1 year later manifested by urethral discharge, balanitis and prostatitis, bilateral conjunctivitis and keratitis and arthritis.

After the third attack described above had subsided the patient remained entirely well except for occasional episodes of slight conjunctivitis until 1 year after discharge, when prostatic massage was performed. Culture of the prostatic

\*We are indebted to D. Fletcher H. Colby of the Massachusetts General Hospital, for permission to report this case, the penitentiary features of which have been reported by him.<sup>10</sup>

†These first two attacks have been reported elsewhere.<sup>11</sup>

secretion was negative for L organisms. Two days later, he noted slight urethral discharge and 1 week later developed bilateral conjunctivitis. During the following week, the right hip and both knees became painful. On examination the conjunctivas of both eyes were markedly inflamed. The right hip was painful, and both knees contained effusions. Prostatic cultures showed an abundant growth of L organisms and a few staphylococci but no gonococci. The urethritis and conjunctivitis subsided in 2 weeks, but during the following 2 months, he continued to have intermittent attacks of pain, swelling and tenderness of wrists, knees and left first metacarpophalangeal joint. Roentgenograms showed moderate decalcification of the bones around the knees and wrists. At the end of 2 months, streptomycin was obtained, and the patient received 21.5 gm in 6 days. Subsequently, he had no further recurrence of joint symptoms though the sedimentation rate remained slightly elevated for 3 months.

Thereafter, he continued to feel well until 3 months later, when he noted stiffness and swelling of the left knee. Four days later there was recurrence of slight urethral discharge and on the following day slight conjunctivitis. On examination 5 days later, the left knee and the interphalangeal joint of the right first toe were hot, red, very painful and swollen. There was a severe conjunctivitis, with purulent discharge, and a slight urethral discharge. Cultures of the urethral discharge and of the urine showed a moderate growth of L organisms and a few colon bacilli and *Staph. albus* and *Staph. aureus*. Roentgenograms showed persistence of slight decalcification of the bones around the knees. The patient was treated with streptomycin in a dosage of 4 gm a day for 13 days. The urethritis and conjunctivitis subsided within 1 week, but swelling of the left knee persisted for 2 months. The sedimentation rate has remained slightly elevated for the past 5 months.

### DISCUSSION

The observation that human beings may harbor organisms belonging to a group that includes several important animal pathogens is in itself interesting. Interest is heightened by the fact that these pleuropneumonia-like organisms appear to be pathogenic to human beings. The most definite indication of pathogenicity has been obtained from the study of male patients. The fact that all the patients in this series had urethritis, prostatitis or cystitis suggests that the organism is pathogenic for the genitourinary tract. Most impressive were the patients with cystitis, such as Case 11, in whom the L organisms were present in pure culture for a long period and decreased markedly or disappeared from the urine as the clinical symptoms subsided. Further indication of the pathogenicity was obtained from one of the patients with Reiter's syndrome (Case 12). L organisms were cultured from the prostatic secretion at the onset of three separate attacks of the disease and were not found in the interval between the episodes.

The presence of acute joint involvement in 27 of the 58 men with positive cultures for L organisms suggests pathogenicity for synovial tissues as well as the genitourinary tract. In 2 patients with Reiter's syndrome, organisms were cultured from the synovial fluid. This association with joint disease is of particular interest because joint involvement is a common feature of the diseases produced by the pleuropneumonia group of organisms in animals.

The evidence of pathogenicity gained from the study of female patients is more equivocal. The relatively high incidence of L organisms in the

female genitourinary tract suggests that they are part of the normal bacterial flora in this location. On the other hand, their presence in various inflammatory processes of the genitourinary tract either in pure culture or in much greater abundance than other bacteria suggests that they are at times pathogenic.

In evaluation of the evidence gathered to date it should be remembered that some strains are presumably not recovered by the present methods, and that the strains isolated probably belong to more than one species and differ in their pathological significance. The fundamental biologic study of the organism obtained from human beings is still in a primitive stage. The cultural methods, which at present are the only means of recognition, are probably inadequate. Attempts are now being made to develop biologic methods, such as serologic and skin tests. The need for a more detailed study of the properties of the various strains, especially their serologic characteristics and their pathogenicity, is indicated by the observations that attest to their ability to cause disease in human beings.

Further difficulty in evaluating the role of pleuropneumonia-like organisms arises from the fact that some of the bacteria commonly found in human beings grow in an L variant form under certain cultural conditions, as in the presence of penicillin. Because of this difficulty, the 8 male patients with severe urinary-tract infection in whom L organisms were found only after the growth of other bacteria was suppressed either by addition of penicillin to the medium or by treatment of the patient with penicillin or streptomycin have not been included in the present series. It is impossible to assess the significance of the L organisms in these cases. It seems probable that they represent one of the many organisms that together cause the urinary-tract infection. However, they may be variant forms of the other bacteria present in the inflamed urinary tract.

### SUMMARY

The properties of pleuropneumonia-like organisms (L organisms) and the methods used for their isolation and identification are briefly described.

Pleuropneumonia-like organisms were present in 58 of 222 routine specimens (26 per cent) from the uterine cervix and vagina and may be part of the normal bacterial flora in these locations. Suggestion of possible pathogenicity, however, was provided by their recovery from inflammatory processes of the female genital tract.

Pleuropneumonia-like organisms were found in only 6 of 71 routine specimens from the male genitourinary tract. Evidence of their pathogenicity was more definite than that in women, since all 58 patients of this series from whom positive cultures were obtained had urethritis, prostatitis or cystitis. In 6 of the 9 cases in which the

infection extended into the bladder the organisms were obtained in pure culture from the urine. Gonococci and L. organisms were found simultaneously in only 2 male patients.

Material from other sources, including the respiratory and gastrointestinal tracts and cerebrospinal fluid, was examined by similar methods but with negative results except in synovial fluids from 2 patients with Reiter's syndrome.

Eighteen of the 58 male patients with genitourinary-tract infections had an acute type of arthritis when the cultures were positive for L. organisms. Nine of these men had simultaneous urethritis, conjunctivitis and arthritis, the syndrome characteristic of so-called Reiter's disease. In 1 patient L. organisms were found in the prostate during three attacks of the disease.

These observations indicate that pleuropneumonia-like organisms have pathogenic activity in the genitourinary tracts of men and women and may be related etiologically to an acute infectious type of arthritis and to Reiter's syndrome.

We are indebted to the following physicians for permission to include cases in this series: Drs F. Albright, J. D. Barney

W. W. Beckman, R. Chute, F. H. Colby, L. W. Kane, S. B. Kelley, S. McGinn, L. S. McKinnick, J. V. Meigs, L. Parsons, C. L. Short and H. T. Suby of the Massachusetts General Hospital; Dr R. L. Berg of the United States Naval Hospital, Chelsea; Drs T. H. Flynn and A. H. Mayby of the United States Marine Hospital, Brighton; Dr J. A. McLaughlin, Naval Air Station, Squantum; Dr T. A. Warthin, Veterans Administration Hospital, West Roxbury; and Cushing Veterans Administration Hospital, Framingham.

Eight of the cases of this series have been included in other papers:<sup>11, 12, 13</sup> Seven others will be reported by Berg and McLaughlin.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., Editor

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### CASE 34161

#### PRESENTATION OF CASE

A three-and-a-half-month-old male infant entered the hospital because of persistent diarrhea.

The birth weight was 6 pounds, 3 ounces, and a statement was made that the baby was blue at birth. However, he gained weight at a normal rate, ate well, and seemed normal in every way except that when he cried or breathed rapidly some cyanosis appeared. There had never been any convulsions, hematuria, vomiting or jaundice.

Four weeks prior to entry the patient developed a cough and coryza, and had several bouts of what were said to be projectile vomiting. Four days later he was taken to another hospital, where a diagnosis of bronchopneumonia was made. X-ray films at that time showed the heart to be to the right of the sternum and an additional diagnosis of congenital heart disease was made. He remained in the hospital and ten days before admission to this hospital

he developed a persistent and moderately severe diarrhea (ten to twelve bowel movements per day). Several of the other infants on this ward also developed diarrhea at about the same time. Five days before admission the diarrhea became much severer, and penicillin therapy was started. Because of the persistent diarrhea the patient was transferred to this hospital.

Physical examination revealed a marasmic and cyanotic infant. He appeared to be fairly well hydrated. Cyanosis was present to a mild degree but was considerably intensified when the patient cried. The chest was clear to percussion and auscultation. The heart was percussed to the right of the sternum and the point of maximum impulse was in the fifth interspace 4 cm. to the right of the sternum. The rhythm was normal, and the rate was 140. There was a soft, Grade II systolic murmur heard best in the third interspace to the left of the sternum.

Examination of the blood disclosed a red-cell count of 4,740,000, with a hemoglobin of 14 gm., and a white-cell count of 7500, with 88 per cent neutrophils. The urine was normal. Blood cultures were negative, and cultures of the stool showed no significant organisms. A blood Hinton test was negative. A tuberculin test in a dilution of 1:1000 was negative.

Soon after admission the number of daily bowel movements decreased markedly, until they became normal. On the third hospital day the child had an episode of severe cyanosis associated with vigorous respiratory activity. The trachea was suctioned, and much thick white mucus was recovered. The patient recovered entirely within fifteen minutes.

The next day a swallow of lipiodol was given, and x-ray examinations showed no evidence of an esophagotracheal communication. The lipiodol passed down the esophagus into the stomach, which lay in normal position on the left side. There was no evidence of constriction of the esophagus. There was a slight indentation opposite the arch of the aorta, which seemed to indicate that the aorta descended on the left side. There was also a ques-

dural taps were done on the eighth day, without return of fluid. On the fourteenth day the temperature began to spike up to 102°F. The white-cell count was 10,900. Physical examination showed a questionable decrease in the percussion note over the left lower lobe. Because he was not taking his feedings very well, the patient had been started on stomach-tube feedings. On the twentieth hospital day, immediately after one feeding, he began to cough, became cyanotic, breathed very rapidly, and died, despite attempts at suction and artificial respiration.

#### DIFFERENTIAL DIAGNOSIS

DR FRANCIS McDONALD Will Dr Wyman please demonstrate the films?

DR STANLEY M. WYMAN The best demonstration of the esophagus is shown by the opaque tube, which extends through the esophagus into the stomach on the right side. The heart is seen on the right.

DR McDONALD "There was a slight indentation opposite the arch of the aorta, which seemed to indicate that the aorta descended on the left side."

DR WYMAN That is suggested on one of the spot films. However, a better look at the plain film with the tube in place shows a considerable shadow to the right of the esophagus and trachea, which makes me think that the aorta actually descends on the right side rather than on the left. I think that the observation of the left-sided aorta is perhaps inaccurate. The filling defect I cannot identify. There is good filling of the esophagus in this portion. I can detect no true abnormality from the films, which are not satisfactory and are noncontributory. The chest films show that the heart is in the right side of the chest, with the apex pointing to the right. The heart is not grossly enlarged. The pulmonary-vascular shadows are decreased in prominence. There is some multiple increased density in the left lung field medially. I should think that this was some sort of pneumonic process. It is seen on the other films consistently. We can therefore say that the heart is not grossly enlarged and lies on the right side (a dextroposed heart), the pulmonary vascular shadows are decreased in prominence and there is presumably some congenital anomaly.

DR RONALD C. SNIFFEN The liver is on the right side?

DR WYMAN Yes, it is on the correct side.

DR McDONALD Was the mucus removed by the bronchoscope cultured?

DR CHARLES U. LOWE It was cultured and yielded *Staphylococcus aureus*.

DR McDONALD I would welcome expert advice on the electrocardiogram.

DR SNIFFEN I do not believe there is anyone here who can give it.

DR McDONALD It sounds like a relatively clear-cut interpretation. About the only mistake that might be made is transposition of the arm electrodes.



FIGURE 1 Roentgenogram, Showing the Apex of the Heart in the Right Midclavicular Line

tionable filling defect just above the aortic arch as seen on the anteroposterior view. The lung fields were essentially clear, without evidence of active disease. The pulmonary vascular markings throughout seemed to be decreased. The apex of the heart lay in the right midclavicular line (Fig 1).

On the sixth hospital day the patient had a cyanotic episode, much the same as the previous one. However, suction did not relieve the attack, and a laryngoscope and then a bronchoscope were passed and a small amount of mucus was removed. After oxygen had been administered for some time the patient was able to breathe somewhat more easily, but there was still considerable forcefulness to the respiratory movements and some retraction of the interspaces. Because of the presence of bubbling rales at the lung bases sulfadiazine and penicillin therapy were instituted. An electrocardiogram was interpreted as being consistent with dextrocardia. The spinal fluid was not remarkable. Bilateral sub-

I am not a cardiac expert, so that for the interest of the group, I shall quote from Taussig's\* book.

Lead I is in the mirror image of normal. Leads II and III replace each other. In Lead I both P waves and the T waves are normally inverted and the principal deflection of the QRS complex is downward. The findings in Lead III are those usually seen in Lead II and the form of deflection in Lead II is similar to that seen normally in Lead III.

DR SNIFFEN The interpretation of the electrocardiogram was as follows: "The tracing is consistent with dextrocardia and inverted Lead I and interchanged electrodes 2 and 3 give normal axis and T waves."

I might say that the child did much better in an oxygen tent than is indicated in the record.

DR McDONALD It seems as if we have two main categories for diagnosis here. One is infection. We have an infant in an age group that is immunologically immature, subject to invasion by colon bacilli, staphylococci, influenza bacilli and other organisms, in addition to the usual streptococcal and pneumococcal invaders of the respiratory tract. It is extremely important in this age group to obtain blood cultures (using pour plates and broth flasks) and cultures of coughed-up secretions to obtain a precise idea what the organism is and to govern therapy accordingly. This patient was given sulfadiazine and penicillin, probably on that basis. *Staph aureus* was obtained on one attempt and cannot be passed off as a contaminating organism, as it frequently may in an adult group. *Staphylococcus* may be an invading agent in this age group. The cough, the dyspnea, the course and the x-ray findings, which might possibly be consistent with an early atelectasis or bronchiectasis as well as pneumonia, make me conclude that the baby did have pneumonia. The second diagnosis is a definitely proved cardiac abnormality. I believe that we can take the word of Dr Wyman that displacement of the heart was not likely from any of the physical findings or x-ray evidence. The electrocardiogram of dextrocardia is a conclusive finding. The presence of dextrocardia without situs inversus markedly increases the likelihood of associated anomalies. We can therefore assume that, in addition to the dextrocardia, either there were anomalies of the heart itself or, if by chance the aortic arch was on the left side, there was a good likelihood of anomalies of the vessels at the base of the heart. As may be seen in this case, the heart is twisted around, with the aortic arch where it should be normally, with the corresponding difficulty in readjustment of the vessels at the base. In addition to the diagnosis of dextrocardia without situs inversus I shall say question of pulmonary stenosis, question of single ventricle and question of anomaly of vessels at the base of the heart.

DR SNIFFEN You took care of this patient, Dr Lowe. Have you anything to add?

DR LOWE There are two things that might be clarified—first of all the difficulties with inspiration, the cyanosis usually followed feeding, which strongly suggested vascular anomaly at the base of the heart. The second point is that it was obvious that oxygen helped the child, which is unusual in children with cyanotic heart disease.

DR RICHARD SCHATZKI Is it not likely if a baby is short of breath that feeding usually makes the difficulty worse?

DR LOWE The child was not short of breath normally. The extreme attacks described in the record

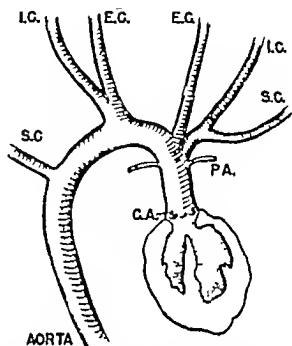


FIGURE 2. Drawing of the Heart and Great Vessels Showing Persistent Truncus, Patent Interventricular Septum, Tricuspid Semilunar Valve, Pulmonary Arteries from Truncus, Persistent Fifth Aortic Arch on the Left and Right Sided Aorta.

occurred seven times while the child was in the hospital, and the last one was fatal. Dyspnea was not part of the general picture.

#### CLINICAL DIAGNOSES

Asphyxiation due to aspiration of feeding  
Persistent double aortic arch  
Dextrocardia  
Pneumonia  
Congenital heart disease

#### DR McDONALD'S DIAGNOSES

Pneumonia  
Dextrocardia  
? Single ventricle  
? Pulmonary stenosis  
? Anomaly of vessels at base of heart.

#### ANATOMICAL DIAGNOSES

Right-sided aorta  
Persistent truncus arteriosus  
Patent interventricular septum  
Persistent fifth aortic arch on left  
Acute purulent bronchitis with early bronchopneumonia

\*Taussig, H. B. *Congenital Malformations of the Heart*. 618 pp. New York: Commonwealth Fund, 1947.

## PATHOLOGICAL DISCUSSION

DR SNIFFEN At the time of death the patient was somewhat emaciated and cyanotic. The abnormal findings were confined to the heart and lungs. In the lungs there was a generalized purulent bronchitis most marked in the left lower lobe. This was accompanied by a mild peribronchial inflammatory infiltration involving the alveolar walls and septums. On the left side there was a fibrinous and fibrous pleurisy without effusion. A small amount of mucus and aspirated gastric contents were found in the trachea and major bronchi. The apex of the heart lay in the right midclavicular line. The pericardium and myocardium were normal,

arteries, which were not over 1 mm in diameter. The ductus arteriosus was not patent. Then, as one proceeded distally along the arch of the aorta, just beyond the left pulmonary vessel, an arterial trunk left the aorta. This trunk divided immediately into two branches, the first giving rise to the left subclavian and internal carotid arteries, and the second to the left external carotid artery. The next aortic branch was the right common carotid artery, with its external and internal divisions, and the last major vessel to leave the aortic arch was the right subclavian artery.

We believe that these structural abnormalities were the results of the disintegration of the first

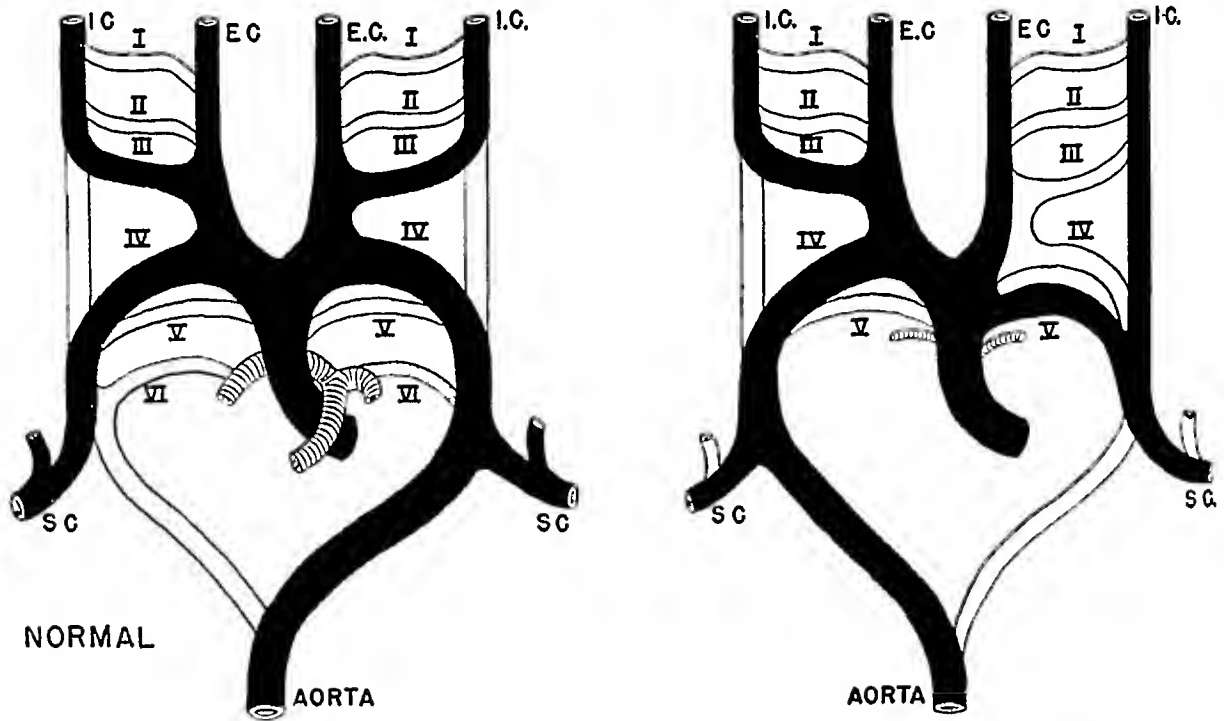


FIGURE 3 Drawing, Showing Disintegration of the First Four Aortic Arches on the Left, with Persistence of the Fifth Aortic Arch

the latter measuring 4 mm in each ventricle. The heart was slightly enlarged.

The dissection of maldeveloped hearts is confusing, since minor structural variations change the interpretation of the developmental abnormalities a great deal. I shall demonstrate several diagrams so that I will not become snarled in the mechanics of the arterial abnormalities.

The first is a drawing of the heart and great vessels in this child (Fig 2). The heart showed a persistent truncus, and as might have been expected with this anomaly, there was a defect in the membranous septum between the ventricles. The truncus overlay both ventricular chambers, but mainly the right ventricle. The outlet was guarded by three normal semilunar valve cusps of equal size. The coronary vessels followed the usual course. There was a right-sided aorta. The first branches to arise from the truncus were two minute pulmonary

four aortic arches on the left side, with persistence of the fifth aortic arch (Fig 3). The reason for this opinion is the fact that the main trunk on the left side was very short. If it were long, we could be confident that the fourth arch had persisted after the disintegration of the first three arches. Furthermore, this main trunk arose immediately distal to the left pulmonary artery. On the right side the fourth arch and dorsal aorta had persisted to form the main arterial trunk.

The formation of three equal semilunar cusps in the truncus is difficult to understand. One would expect four cusps of equal size or unequal size or three unequal cusps. In fact the truncus had the structure of a normal aorta.

As a sidelight, the left lung was divided into three lobes, and the right lung had only two lobes.

No constrictions were found in the esophagus, and the abdominal organs were in the normal position.

## CASE 34162

## PRESENTATION OF CASE

A forty-eight-year-old chauffeur entered the hospital because of pain in the right elbow.

One year before entry the patient had a painful right upper arm for a few weeks following a strain in breaking a fall. He recovered completely from this episode, however, and remained asymptomatic until one month before entry, when he slipped and twisted the right arm while shoveling snow. He immediately sustained severe pain around the elbow, with radiation to the outer aspect of the right shoulder. The pain gradually subsided and disappeared a week later, when he first noted swelling of the "muscles" just above the elbow. Two weeks before entry physical examination and x-ray studies demonstrated a "tumor" of the lower humerus. One week later he slipped and fell and felt a crack in the arm, with resulting severe pain. X-ray films were taken, the arm was splinted, and he was sent to this hospital.

His father had died of carcinoma of the liver, and an uncle had carcinoma of the stomach.

The patient allegedly had enjoyed excellent health and denied weight loss, systemic symptoms, previous trauma or bone disease.

Physical examination revealed a well developed and well nourished man with moderate pitting edema below the lower third of the humerus, a swelling around the elbow and a soft-tissue mass, 2.5 by 5 cm., above the medial epicondyle, in the region of which there seemed to be some abnormal mobility. There was no discoloration of the skin and no evidence of motor or sensory impairment. A few firm, nontender lymph nodes (0.5 to 1.0 cm in diameter) were palpated bilaterally in the groin. No abdominal masses or chest abnormalities were demonstrated.

The temperature was 98°F, the pulse 76, and the respirations 15.

Examination of the blood showed a hemoglobin of 15.1 gm per 100 cc. and a white-cell count of 11,400, with 79 per cent neutrophils. Urinalysis was negative. No Bence-Jones protein was found.

X-ray films of the right humerus demonstrated a destructive process 10 cm long in the distal third through the entire thickness of bone but with no spicule formation, no new-bone formation, and no periosteal elevation, there was a pathologic fracture through this area. The medulla above the lesion had some irregular areas of mottling, and the cortex appeared roughened (Fig 1). Scout films of the chest, spine, pelvis, left arm and both legs were normal.

An operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR CLIFFORD C FRANSEEN In the differential diagnosis of any suspected bone tumor, Dr Channing Simmons has taught us to review the history and

the signs and symptoms from three aspects: infectious, metabolic and neoplastic. The age (forty-eight years) is important to consider, as it is in any case of suspected bone tumor, and I shall deal with this later. This man either led a precarious existence or was very clumsy, because he suffered so many injuries from falls. Possibly, a neurologic examination would have thrown some light, but we do not have this information.

Let us consider infectious lesions first. With respect to osteomyelitis, the temperature was normal, and there was no suggestion of local inflammation. The record does not suggest a chronic inflam-



FIGURE 1

matory lesion, such as Brodie's abscess, especially by x-ray study. There was a slight elevation of the white-cell count, but little else to suggest that this process had arisen on the basis of osteomyelitis. In the latter lesions, also, enough reactive new-bone formation usually accompanies the osteomyelitis so that pathologic fracture is uncommon.

Syphilis must be considered only because it can simulate practically any bone lesion. The blood Hinton test is not given. We do not know whether or not it was taken, but, of course, it should be included in any study of a bone lesion. Syphilis, as a rule, produces considerable periosteal reaction, which was minimal or absent in this case. Tuberculosis can only be mentioned — we cannot rule it in or out in this case except for the statistical rarity of an isolated lesion in the humerus, especially since the chest film was normal.



We must consider the neoplastic group of diagnoses more seriously. The character of the destruction suggests that this was a neoplastic lesion, and probably a malignant one. Benign tumors that should first be considered are lesions such as bone cysts. They usually occur in the young age groups, and usually the first knowledge of their presence is the occurrence of pathologic fracture, unless they are picked up incidentally by an x-ray examination. It would be unusual for a man of this age to have one. A giant-cell tumor may remotely be suggested by the x-ray film, but the site in the bone is not a usual one. Perhaps we should see the x-ray films, since their interpretation becomes more important from now on.

DR STANLEY M. WYMAN: The lesion described lies in the lower third of the humerus (Fig. 1) but does not extend down to the condyles. It seems to be a purely destructive process. There is no visible new-bone formation and no evidence of periosteal reaction. The roughening of the cortex is seen on either side of the shaft, much higher on the humerus. The spine, both femurs and the bones of the pelvis and lumbar spine show no definite disease. The lung fields are clear, the heart is not remarkable. I cannot make any statement about the abdominal viscera. The film is not of diagnostic quality.

DR FRANSEEN: Is the mottling in the center merely an area of irregular bone destruction, with no evidence of trabeculation?

DR WYMAN: I interpret the mottling as bone destruction, with residual areas of medullary trabeculation and some areas of residual cortex remaining between the areas of destruction. I think the process may have started centrally and extended to involve the entire thickness of the bone.

DR FRANSEEN: The x-ray appearance is different from what I had visualized from the written description. I did not appreciate that the periosteal reaction was so far away from the main lesion.

To continue the discussion, I can say that I am not familiar with any giant-cell tumor that has taken on an appearance such as this even when a pathologic fracture has occurred through it. If we, then, go on to consider other primary malignant tumors, Ewing tumor must be thought of. In this respect, again, the age of the patient is very important. I know of no case of Ewing tumor in this age group, but as in any bone lesions, it can perhaps occur. I met Dr Simmons just before this conference and asked him if he remembered any patient with Ewing tumor in this man's age group, but he could remember none. Geschickter and Copeland\* have reported no case in a patient so old as this man. We have all seen bizarre x-ray pictures in Ewing tumor, but there is no suggestion here of lamination of the periosteum or the other signs that are usually

associated with this tumor. As you perhaps know, at least 50 per cent occur in adolescence, with tapering off of the age incidence at either end. The tumor rarely occurs in the thirties. Age in itself is a strong argument against a Ewing tumor in this case, but, again, one cannot exclude it entirely.

Multiple myeloma should be considered, but this patient at forty-eight is not too good a candidate for it. This lesion is not the purely destructive lesion by x-ray study that one usually associates with multiple myeloma, and to have an isolated lesion in an extremity without evidence elsewhere would be extraordinary in multiple myeloma. In this disease the serum protein is sometimes elevated, but we do not have this determination to help us. The character of the patient's pain, which showed remissions between aggravations by trauma, is suggestive of multiple myeloma in a general way, but these are about the only facts I can find in its favor. There was no Bence-Jones protein in the urine and no evidence of nephritis on urinalysis, the latter frequently accompany the lesion. So much for multiple myeloma.

Considering other malignant bone tumors, malignant tumors of cartilaginous origin usually show some trabeculation, and this lesion, according to the x-ray interpretation, gave no suggestion of trabeculation, but rather irregular mottled areas of destruction. The osteolytic form of osteogenic sarcoma must more seriously be considered in a destructive lesion such as this appeared to be. There was not enough new-bone formation to consider the osteoblastic form of osteogenic sarcoma. The osteolytic form can begin subcortically and, as it gets larger, extend to a more central position, as in this case. Pathologic fracture, as in this case, is common. However, osteogenic sarcoma, as Dr Simmons has pointed out so frequently, is uncommon at this age unless associated with Paget's disease. However, there is some overlapping of age groups, and osteolytic sarcoma cannot be excluded on the basis of age alone. Reticulum-cell sarcoma must also be considered, and I would be unable definitely to exclude this lesion without a biopsy. I see no reason to consider other bone-destructive lesions such as eosinophilic granuloma. I have had no personal experience with them, but know that they usually occur in much younger age groups, particularly in children.

In the neoplastic group, we are then left to consider secondary or metastatic lesions of bone. A secondary lesion of Hodgkin's disease taking this form, without any other evidence of it elsewhere, would be very uncommon because bone involvement of this type would usually occur only in late stages of the disease. I think we can disregard the lymph nodes described in the groins, because, in my experience, nodes of this description can be felt in almost any person, so that I see no reason for considering Hodgkin's disease seriously.

\*Geschickter, C. F., and Copeland, M. M. *Tumors of Bone*. 709 pp. New York: American Journal of Cancer, 1931. P. 640.

I think, however, that metastatic carcinoma must be considered very seriously, since the picture is entirely consistent with that diagnosis. In a woman, the breast would, of course, be regarded as a primary source, but this man's breast was presumably easily examined, and a carcinoma would have been discovered if present. The most common sources to consider in this case are the prostate and kidneys. Metastases from prostatic carcinoma are apt to show more osteoblastic activity than this lesion did, but some that we have seen have been almost completely osteolytic. An isolated metastasis like this in an extremity is uncommon in carcinoma of the prostate. Renal-cell carcinoma frequently produces a soft, pulsating tumor. In this case there is no description of the consistence of the tumor. The few that I have seen have been confined especially to the sternum and upper end of the humerus. This site, in the lower end of the humerus, is more unusual. The metastases from renal-cell carcinoma are often a more expanding type of tumor than this — this tumor mass was only 2.5 by 5.0 cm. That is as far as I can go, since nothing is said in the record about examination of the prostate or kidneys.

I had the impression as I first read through the record that the most likely diagnosis would be an osteolytic form of osteogenic sarcoma. On looking at the x-ray films, however, a metastatic lesion seems more likely. In any lesion like this, we have been taught that the only approach is to consider it a malignant lesion of bone until proved otherwise, and that the only method by which an exact diagnosis can be made is by biopsy with preparation for amputation if the lesion proves to be malignant. If I have to make a definite diagnosis from the appearance of the x-ray film, I say that this was probably metastatic carcinoma, and that is as far as I am willing to go.

#### CLINICAL DIAGNOSIS

Sarcoma, (?) reticulum-cell type

#### DR. FRANSEEN'S DIAGNOSIS

Metastatic carcinoma

#### ANATOMICAL DIAGNOSIS

Metastatic renal-cell carcinoma

#### PATHOLOGICAL DISCUSSION

DR. ENWIN F. CAVE: I saw this man after he had been admitted to the Baker Memorial Hospital. He was wearing a splint on the right arm. He had a fracture through the diseased area of the lower end of the humerus, and a good deal of swelling of the distal end of the arm and elbow. We could not make an accurate diagnosis, so we did a biopsy, separating the muscles, which were edematous.

The radial nerve was retracted, and we came into the fracture line. The bone was spongy and rather necrotic, the medulla was easily entered, and we took specimens from the cortex, the medulla and the periosteum. An attempt was made to do frozen sections at the time, but nothing conclusive was determined from the sections, so we closed the wound and waited for a report.

DR. TRACY B. MALLORY: The tumor in this case was extensively necrotic, and not until the permanent sections were cut were we able to find areas suitable for diagnosis. When we finally got some viable tumor it was quite evident that we were dealing with carcinoma, with large, clear, vacuolated cells very strongly suggestive of renal origin. Will you go on from there, Dr. Cave?

DR. CAVE: We debated then whether we should study the patient further by doing an intravenous pyelogram. Dr. Grantley Taylor was asked to see him, and he agreed that amputation was indicated and we proceeded with that. Amputation was done about two weeks after the biopsy. We amputated through the surgical neck of the humerus. The wound healed primarily. After that Dr. Chute and Dr. Colby saw the patient, and renal studies were done.

DR. MALLORY: Dr. Wyman, will you show the pyelogram?

DR. WYMAN: The pyelogram shows a tumor in the upper portion of the kidney, displacing the calyces.

DR. RICHARD CHUTE: I was presented with this problem on account of the fact that a number of cases have been reported in which a solitary metastasis from a renal-cell carcinoma has been removed and later the original source found and removed, and the patient remained "cured" for a good number of years. It seemed to us reasonable to extirpate the focus, therefore, Dr. Soutter and I did a nephrectomy. Dr. Soutter might like to say something about the technic and the result.

DR. LAMAR SOUTTER: This is the third case of a transthoracic nephrectomy done in this hospital for carcinoma. The reason for using this approach is that it provides more room for radical surgery. The exposure is better to cut the renal vein on the right side of the spine and the renal artery at the aorta and to remove the regional lymph nodes and the adrenal gland. That was done in this case.

DR. MALLORY: The amputated arm showed a mass of necrotic tumor, again with recognizable areas of renal-cell adenocarcinoma, and the resected kidney showed characteristic hypernephroma. The tumor was extensive enough to have invaded the renal vein and extended along nearly two thirds of the way to the vena cava as they often do.

The patient is still convalescing on the wards and is doing well.

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## FEDERAL SUPPORT FOR MEDICAL EDUCATION

"THE philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow" Half a century ago Osler<sup>1</sup> thus indicated the fluctuations of thought with which men sometimes measure their problems and devise their solutions. The problems are always vivid and immediate, whereas their solutions seem limited — so limited that men find themselves able to move in only one direction or not at all. Wars become inevitable, and so do Government subsidies, but is this wisdom or is it foolishness? Medical education in the United States is today based upon the highest standards in the world and yet whenever it is surveyed it is easily shown to be inadequate and in immeasurable need

of improvement. In a less prodigal age we should have said that we were living far beyond our means, but none is living beyond his means today until he has completely exhausted all chance of Government support. The air is full of talk of such support for medical students, medical research, medical education and medical practice.

The American Academy of Pediatrics has recently released a recommendation for federal support of pediatric education.<sup>2</sup> The figures presented are said to reveal a startling lack of adequate training on the part of those who are caring for children. On the other hand if such figures were broken down into groups of those whose hospital training or lack thereof was received ten, twenty and thirty or more years ago, it might become apparent that we are on the very crest of a wave of improvement in pediatric training as judged by time spent in pediatric hospitals after graduation from medical school. Certainly there are more candidates than there are opportunities for approved residency training in pediatrics, and in all the other specialties as well. When one turns to the need for more physicians trained in the care of children in the remote and rural areas, fellowships are suggested for medical graduates "committed to return to practice in an area of need." Many have tried, but no good answer has yet been framed for the old question of how they are to be kept down on the farm. The cost of medical education to the student is also cited as a reason why there may be a tendency on the part of young doctors to renounce special training or to settle in the urban areas where professional life may be economically easier. The recommendations are specific that an appropriation of \$5,000,000 be authorized, to be administered by the Federal Security Administration in direct support of pediatric education. Half of this would go to the departments of pediatrics of the approved medical schools in accordance with need and student enrollment. One and a half million dollars is recommended for scholarships and fellowships or other purposes directly related to pediatric education, and \$1,000,000 is recommended for allocation to states in need because of their remote and rural areas into which physicians cannot now be induced to move.

Other specialties occupy educational grounds no less valid and deserving, what would be the tendency for them to generate equalizing pressures? Medical schools are constantly being surveyed by professional groups gathering data about this or that special interest. Such surveys are generally followed by reports indicating the existing inadequacies and suggesting minimum standards. It is as though our leaders were busying themselves by seeking to perfect each small part of a mosaic, but neglecting to concern themselves with the over-all picture or the condition likely to supervene ten years hence.

That the eyes of different groups are not focused upon the same objective is emphasized by recent divergent estimates concerning the likelihood of a shortage of physicians by 1960.<sup>1</sup> The United States Public Health Service and the Federal Security Administration anticipate a shortage of between 30,000 and 50,000 doctors in another decade, whereas the American Medical Association estimates that by 1960 there will be in this country at least 1 physician for every 700 people—a greater ratio than at present or in the immediate past. The number of physicians is increasing at a relatively more rapid rate than that of the population as a whole. This would be all right if there were to be more for them to do in the coming era than there has been in the past. If there are to be vast increases in hospital and research facilities more medical manpower will be needed. On the other hand, too many physicians, like too many cooks, could be a menace to the people's health, especially if it is necessary to sacrifice quality to produce the larger number, and if they must eke out a living by private practice in this apprehensive and neurotic world.

Whether an extension or permanent modification of the present GI bill of rights for all medical students would be helpful (and to whom) is another large subject. Such an extension would not produce more doctors. It might make medical education available to students who would otherwise seek a different training or vocation. It would surely attract the type of student whose hat is in the ring for a scholarship. Medicine has need for the best brains that can be recruited; it also needs character. Brains are more easily measured than character,

but character motivates and guides the application of brainpower, and is therefore recognized as a raw material without which a good doctor cannot be educated regardless of the resources at his disposal. If a formula could be devised that would recognize and attract character as readily as brains are now recognized, medical educators would find the task of selecting students greatly lightened and better performed than at present.

Expansion of federal largess is potentially without limit—but there is a fly in the lard. The members of the medical profession are not unanimously convinced that Government support can be contrived without Government interference. In a recent Washington Report<sup>4</sup> an aide of the Federal Security Administrator is quoted as asking the question: "Why must Uncle Sam ever be suspected, when he lends a helping hand, of having something up his sleeve?" Whoever can answer this question can also tell us whether all this is wisdom or foolishness.

#### REFERENCES

1. Oiler W. Communism in medicine. In *Open issues: Physicians and doctors to medical students: nurses and physicians in medicine*. 389 pp. Philadelphia: P. Blakiston's Son & Co. 1951. Pp. 277-306.
2. Committee for the Improvement of Child Health America. *Academy of Pediatrics, A Recommendation for Federal Support for Pediatric Education*. Unpublished memorandum, dated February 6, 1949.
3. Editorial. Is there shortage of physicians? *J. A. M. A.* 136:626, 1948.
4. Washington Report No. 39 dated March 1, 1948.

#### THE WORLD MEDICAL ORGANIZATION

POSSIBLY unnoticed by many, in the present confused and disturbed condition of the world, was the announcement from the recent Interim Session of the House of Delegates of the American Medical Association in Cleveland on the formation of a World Medical Organization.

This was agreed to in principle at the Atlantic City Annual Session in June, 1947, and authority for participation wholeheartedly voted by the House of Delegates. The organization meeting was held in Paris in September, with four members of the Board of Trustees as the American representatives. One hundred and twenty-five delegates from forty-eight nations attended. From the reports on the sessions, one gathers that some of the meetings resembled those held by the United Nations at Lake Success. Apparently, there were many trying moments when 'patience, tolerance, long-suffering

**FISH** — John E. Fish, M.D., of Canton, died on March 30. He was in his seventy-fifth year.

Dr. Fish received his degree from Dartmouth Medical School in 1896. He was a former president of Norfolk District Medical Society and was formerly superintendent of the Massachusetts Hospital School in Canton. He was a fellow of the American Medical Association.

His widow, two daughters and two sons survive.

**HOSLEY** — Walter A. Hosley, M.D., of Topsfield, died on March 25. He was in his seventieth year.

Dr. Hosley received his degree from Harvard Medical School in 1904.

Two daughters survive.

**HUNT** — Reid Hunt, M.D., of Boston, died on March 7. He was in his seventy-eighth year.

Dr. Hunt received his degree from College of Physicians and Surgeons of Baltimore in 1896. He was associate professor of pharmacology at Johns Hopkins University School of Medicine from 1898 to 1903, chief of the division of pharmacology, United States Public Health Service, from 1904 to 1913 and professor of pharmacology at Harvard Medical School from 1913 to 1936. He was professor of pharmacology, emeritus, Harvard Medical School, a former chairman of the Council on Pharmacy and Chemistry of the American Medical Association and a member of the Association of American Physicians.

His widow survives.

**IRWIN** — Vincent J. Irwin, M.D., of Springfield, died on February 26. He was in his sixty-first year.

Dr. Irwin received his degree from Yale University School of Medicine in 1909. He was a member of the American Academy of Ophthalmology and Oto-Laryngology and a fellow of the American Medical Association.

His widow survives.

**LELAND** — Leslie P. Leland, M.D., of Worcester, died on March 16. He was in his sixty-fourth year.

Dr. Leland received his degree from Boston University School of Medicine in 1909. He was a former secretary of the Worcester District Medical Society and was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow and two daughters survive.

**MAY** — James V. May, M.D., of Belmont, died on December 24, 1947. He was in his seventy-fifth year.

Dr. May received his degree from University of Pennsylvania School of Medicine in 1897. He was a former president of the New England Society of Psychiatry, Massachusetts Psychiatric Society and American Psychiatric Association, and was a fellow of the American Medical Association.

**O'BRIEN** — John C. O'Brien, M.D., of Greenfield, died on March 18. He was in his eighty-fifth year.

Dr. O'Brien received his degree from University of Vermont College of Medicine in 1887. He was formerly a trustee of the Northampton State Hospital, town physician and physician to the Greenfield House of Correction, and was a fellow of the American Medical Association.

A son and a daughter survive.

## MEDICOLEGAL ABSTRACT

**Relation of Patient and Physician — Confidential communications and their possible disclosure in hospital records.** According to the terms of his oath the physician is bound to treat the communications of his patient in confidence. Legally, however, no such privilege existed under the common law. In some states, however, statutes have protected confidences revealed to the physician

for the purpose of adequate diagnosis and treatment. In states where such confidences are protected by statute the question may arise to what extent, if any, the protection is removed if the information revealed to the physician in confidence is made a part of a hospital record. Such a question was recently considered by the Supreme Court of Ohio.

In a proceeding in which it was sought to show that a will was invalid on the ground that the testator lacked the necessary mental capacity, hospital records were offered, consisting of the entrance slip, the physician's direction for the medication to be administered and treatment to be given the patient by the nurses, record of analyses of the blood and the urine of the patient and the day-to-day chart made and kept by the nurses who had charge of the patient while he was at the hospital. These charts recorded the food and medicine given and the condition and behavior of the patient, the fact that he was irrational at times, that he left his bed at unreasonable hours, that on one occasion he used a wastepaper basket as a commode, and that on several occasions he became unruly. Part of the record included notations of increasing administrations of sedatives culminating on the date that the will was signed. These portions of the record were all admitted in evidence. A verdict was returned that the writing in question was not valid as the last will and testament of the deceased, and judgment was entered for the contestant. The contestees sought a reversal on the grounds that the hospital record contained matters communicated confidentially to the physician and nurses of the deceased and should not have been admitted in evidence.

Ohio has statutes establishing a patient-physician privilege and also providing for the admissibility of hospital records, but the statutes do not specify the relation between the two. The court discussed the question whether or not the communications should have been admitted even though it found that the contestees had waived their privilege by permitting the physician to testify completely and without objection to all details of his diagnosis and treatment. However, the court stated:

The courts in most states having Physician-Patient Privilege Statutes similar to section 11494, General Code, generally hold that communications between Physician and Patient, not in the presence of third persons, for the purpose of diagnosis and treatment of the patient, if carried into a private hospital record or chart, remain confidential, and that such part of the chart or record is inadmissible in evidence unless the privilege is waived.

In discussing generally the admissibility of hospital records the court said:

Such a hospital or physician's office record may properly include case history, diagnosis by one qualified to make it, condition and treatment of the patient covering such items as temperature, pulse, respiration, symptoms, food and medicine given, analysis of the tissues or fluids of the body, and the behavior of and complaints made by the patient.

The court drew a line between direct communication and observed facts or information obtained without communication. The difficulties in determining admissibility according to such a line of demarcation are evident. Portions of the record that report diagnosis and directions for treatment do not fall into either of the categories described by the court. Is the diagnosis admissible? And of what use is it to bar the communications on which diagnosis is based when the diagnosis and medication and directions for treatment clearly indicate the substance of the barred communication? In this case, therefore, part of the records included notations of increasing administration of sedatives that would be confidential if related to the physician by the patient but perhaps avoids the privilege when entered on the hospital record as an observed fact.

If the entire hospital record is admissible in evidence the purpose of the statute and of the physician's oath would be nullified, and professional confidence would be limited to unrecorded information (*Wes v. Wes*, 72 N. E. [2nd] 245, 1947).

## MISCELLANY

### AMERICAN COLLEGE OF SURGEONS APPROVES USE OF NURSE ANESTHETISTS

The Board of Regents of the American College of Surgeons at a meeting on February 21 adopted the following resolution:

The American College of Surgeons regards with deep concern the actions of some physician anesthesiologists in giving the impression to the lay public press that it is unsafe for experienced nurse anesthetists to conduct surgical anesthesia. While it supports the increasing tendency of having physician anesthesiologists in charge of surgical anesthesia it deplores at this time any propaganda for the elimination of the trained nurse anesthetist. On the contrary, the American College of Surgeons is of the opinion that, in view of the inadequacy in number of the physician anesthesiologists and in view of the splendid record of achievement of the nurse anesthetists institutions engaged in the training of nurses for this purpose should be encouraged to continue their programs.

### NATIONAL CANCER INSTITUTE

More than \$1,355,818 in federal grants in aid from Public Health Service funds for cancer research and control has been announced by the Federal Security Administration. It was made on the recommendation of the National Advisory Cancer Council of the National Cancer Institute. Another \$8,000,000 in construction grants for new laboratory and clinical facilities has been recommended by the Council.

## NOTE

Dr. Arthur Marvel Laseck, head of the Department of Anatomy, Medical College of the State of South Carolina in Charleston since 1933, has been appointed Waterhouse Professor of Anatomy at Boston University School of Medicine effective July 1. Dr. Laseck will succeed Dr. Jesse LeRoy Conel, a member of the medical faculty since 1923.

## CORRESPONDENCE

### RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held March 18 it was voted to restore the registration to practice medicine to Dr. George J. Orlandi, 20 Charlotte Road, Newton Centre (formerly of 1234 Blue Hill Avenue, Dorchester).

H. QUINBY GALLUP, M.D., Secretary

State House  
Boston

## DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held March 18 it was voted to suspend the registration of Dr. William P. Pratt, 28 Adams Street, Quincy for three months.

H. QUINBY GALLUP, M.D. Secretary

State House  
Boston

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*An Atlas of Anatomy*. By J. C. Boileau Grant, M.C. M.B. Ch.B. F.R.C.S. (Edin.) professor of anatomy in the University of Toronto. Second edition. 4 cloth, 496 pp. with 91 illustrations. Baltimore: Williams and Wilkins Company. 1947. \$10.00.

This atlas was published first in 1943 and reprinted in 1944 and 1945. Dr. Grant to this edition has added more than two hundred illustrations including the wrist, superficial veins of the limbs, the inguinal region, abdominal viscera, suprarenal gland, smooth and the blood supply of the esophagus, stomach, duodenum, pancreas, bile passages, spleen and suprarenal glands. Also the more common dissecting room variations, the epiphyses and schemes of the distribution of the cranial nerves and of the motor nerves to the extremities are considered. A good index concludes the volume. The book is well published in every way. The illustrations and color work are excellent. The atlas is recommended for all medical libraries.

*Overcoming Stammering*. By Charles Pellmar. With a foreword by Frederic Martin, M.D., director of National Institute for Voice Disorders, Bristol, Rhode Island, and director of Speech Clinics, State Department of Education, Rhode Island. 8° cloth, 160 pp. New York: The Beechurst Press. 1947. \$3.00.

Mr. Pellmar, an experienced practicing speech correctionist, analyzes and evaluates current methods of speech correction and treatment. He presents a plan for speech correction of stammering and stuttering based upon the physiology of speech and proper mental hygiene, rather than on the functioning of the speech apparatus. His method may be used in the home by intelligent parents. The text deals with an autobiographic sketch of a stammerer by Aaro Pellmar. A list of books and an index conclude the volume. The book is well published. It is recommended for medical and educational libraries.

*Procedure in Examination of the Lungs with Especial Reference to the Diagnosis of Tuberculosis*. By Arthur F. Kraetzer, M.D., associate attending physician, Lenox Hill Hospital, physician to outpatients, New York Hospital and instructor in medicine (dermatology), Cornell University Medical College. Third edition revised and with a preface by Jacob Segal, M.D., medical director, Los Angeles Sanatorium. Oxford Medical Publications. 8° cloth, 150 pp. with 16 illustrations and 14 plates. New York: Oxford University Press. 1947. \$3.50.

Dr. Segal, in this revision of Kraetzer's manual has brought the subject up to date since the publication of the previous edition in 1935. The text of the second edition has not been disturbed but the new material has been incorporated in an appendix of twenty-two pages and sixteen x-ray plates. An x-ray commentary on the correlation of signs leading to a diagnosis with histories of 13 cases and illustrated with the x-ray pictures is included in the appendix. An index has been added for the first time. The volume is well printed with good type on good paper.

*The Dispensatory of the United States of America* By Arthur Osol, Ph G, M S, Ph D, professor of chemistry and director of the department of chemistry, Philadelphia College of Pharmacy and Science, and George E Farrar, Jr, M D, associate professor of medicine, School of Medicine, Temple University, and chief of Medical Service A, Episcopal Hospital 4<sup>th</sup>, cloth, 1928 pp Philadelphia J B Lippincott Company, 1947 \$16 50

This standard reference work has a remarkable record of one hundred and fifteen years of continuous publication. It was first issued in 1833 as *The Dispensatory of the United States of America*, by Drs George B Wood and Franklin Bache. In 1879, with the fourteenth edition, Dr H C Wood became associated with the elder Dr Wood, and in 1885, with the fifteenth edition, Dr H C Wood became the principal author. With the centennial edition Dr H C Wood, Jr, became the principal author, and he is now advisory editor to this twenty-fourth edition. The work was issued every few years from the beginning, and a number of editions were reprinted, except that editions were not published during the Civil War years, 1859-1864. The text is divided into five parts. Parts one and two, the major portion of the work, describe the drugs recognized by the *United States Pharmacopæia*, the *Pharmacopæia of Great Britain* or the *National Formulary* and the drugs not official in these works. The drugs are listed alphabetically in these two sections. The remaining parts list general tests, processes, reagents and solutions, veterinary uses and doses of drugs, and tables of the *United States Pharmacopæia* or the *National Formulary*. The tables on atomic and molecular weights, and on equivalents of weights and measures are especially valuable. A comprehensive index concludes the volume. The publishing is excellent in every way. Every effort has been made to reduce the weight and size of such a large volume. The text is printed in two columns on a good light paper with a good type. The price is very reasonable for the size of the book. The work is recommended for all libraries, medical and general, and to all persons interested in drugs.

*The Foot and Ankle. Their injuries, diseases, deformities and disabilities* By Philip Lewin, M D, associate professor of bone and joint surgery, and acting head of department, Northwestern University School of Medicine, professor of orthopedic surgery, Post-Graduate Medical School of Cook County Hospital, attending orthopedic surgeon, Cook County Hospital, senior attending orthopedic surgeon, Michael Reese Hospital, and consulting orthopedic surgeon, Municipal Contagious Disease Hospital, Chicago. Third edition 8<sup>th</sup>, cloth, 847 pp, with 389 illustrations. With line drawings by Harold Laufman, M D. Philadelphia Lea and Febiger, 1947 \$11 00

This edition of a standard work has been extensively revised in the light of the vast amount of information gleaned from the records and experience of World War II. Much material has been added, and emphasis has been placed on compound fractures, crushing wounds and osteomyelitis. There is a special chapter on the military aspects of foot and ankle disorders. The sections on traumatic gangrene and amputations have been enlarged, and ringworm has been considered not only as a primary and sole infection but also as a complication of injuries. There is a special chapter on psychosomatic medicine as it relates to certain orthopedic conditions. The book is well published and is recommended for all medical libraries and to all persons interested in the subject.

*Diseases of the Nose, Throat and Ear* By William L Ballenger, M D, and Howard C Ballenger, M D, associate professor and acting chairman, Department of Otolaryngology, Northwestern University School of Medicine, Chicago, and surgeon, Department of Otolaryngology, Evanston Hospital, Evanston, Illinois. Assisted by John J Ballenger, M D, research fellow in otolaryngology, Northwestern University School of Medicine, Chicago. Ninth edition 8<sup>th</sup>, cloth, 993 pp, with 597 illustrations. Philadelphia Lea and Febiger, 1947 \$12 50

This edition of an authoritative textbook has been revised by the addition of much material. Obsolete material has been deleted, and portions of the text rewritten and amplified. There is a new chapter on "headaches and neuralgias of the face," and rhinoplastic reconstruction has been described. The special contributors have revised the chapters on arytenoidectomy for bilateral paralysis of the current laryngeal nerves,

physiology and functional tests of the labyrinth and inflammatory diseases of the labyrinth and peroral endoscopy. The volume is well published in every way. The printing of a history of the editions on the back of the title page would be of value to reviewers and other interested persons. The book is recommended for all medical reference collections.

*Textbook of General Surgery* By Warren H Cole, M D, professor of surgery and head, Department of Surgery, University of Illinois College of Medicine, and director of surgical service, Illinois Research and Educational Hospitals, Chicago, and Robert Elman, M D, professor of clinical surgery, Washington University School of Medicine, assistant surgeon, Barnes Hospital, associate surgeon, St. Louis Children's Hospital, and director of surgical service, H G Phillips Hospital, St. Louis. Fifth edition 8<sup>th</sup>, cloth, 1160 pp, with 558 illustrations. New York D Appleton-Century Company, 1948 \$11 00

This standard textbook, first published in 1939 and last revised in 1944, in this new edition has been thoroughly revised to date. The type has been completely reset, and the volume repaged. The chapters on war and catastrophe surgery, surgical diseases of the chest and chemotherapy have been rewritten. The chapter on the nutritional requirements of surgical patients has been considerably expanded. A chapter has been added on surgical convalescence, including preoperative and postoperative care. The text is well written, and the material well organized. Selected references are appended to each chapter. Indexes of authors and subjects conclude the volume. The publishing is excellent except that the coated paper makes the volume heavy for its size. It is recommended for all medical libraries and all surgeons.

*A Text-Book of Bacteriology* By R W Fairbrother, M D, D Sc (Man), F R C P (Lond), director of the department of clinical pathology, Manchester Royal Infirmary, and special lecturer in bacteriology, University of Manchester. Fifth edition 8<sup>th</sup>, cloth, 480 pp, with 34 tables and 6 plates. New York Grunc and Stratton, 1948 \$6 50

This textbook, first published in 1937, and last revised in 1946, has gone through twelve printings of the five editions, a fact that attests its soundness as a textbook for students. The author has made a thorough revision of the text for this fifth edition. The book is an outline of the medical aspects of bacteriology. The material is divided into three parts: general bacteriology, systematic bacteriology and general technique. A good index concludes the volume, which is well printed with a good type by the lithographic process on light paper.

*Blood Pressure and Its Disorders, including Angina Pectoris* By John Plesch, M D, Budapest, M D, Germany, L R C P and S Edin and Glas. Second edition revised and enlarged 8<sup>th</sup>, cloth, 307 pp, with 125 illustrations. Baltimore Williams and Wilkins Company, 1947 \$6 00

Dr Plesch has revised this second edition of his monograph, first published in 1944, by the addition of material, chapters and case histories. Selected references have been appended to each chapter. The text represents the author's personal experience and research, and is not intended as a comprehensive treatise on the subject. The printing was done in Great Britain and is excellent. The type and paper are good. The book should prove useful to physicians interested in the subject.

*Biochemistry for Medical Students* By William V Thorpe, M A (Cantab), Ph D (Lond), reader in chemical physiology, University of Birmingham. Fourth edition 8<sup>th</sup>, cloth, 496 pp, with 36 illustrations. Baltimore Williams and Wilkins Company, 1947 \$5 00

This English textbook, first published in 1938, and last revised in 1943, has been revised to date. A chapter on the use of isotopes in biochemical investigations has been added, and the sections on protein structure, coenzymes, flavoproteins, bile pigments and nutrition in wartime have been largely rewritten. The text is well written, and the material well organized. The type, printing and paper are excellent. The book should prove useful as an excellent summary of the subject.



*Malaria, with Special Reference to the African Forms.* By W. K. Blackie M.D., Ph.D., F.R.C.P. (Edin.), D.T.M. & H. 8°, cloth 104 pp., with a color plate. Cape Town: The African Bookman for the Post-Graduate Press 1947 10s.6d.

This concise monograph presents the latest methods of treatment with quinine and the newest plasmodial drugs including mepracine (atabrine), pamaquin and paludrine. The first chapter comprises a short historical review, followed by chapters on the parasitology, pathology, clinical features, diagnosis, prognosis, treatment and prophylaxis of the various types of the disease. The material is well organized and well published in every way. The color plate depicting the various plasmodiae is excellent. A good index concludes the text. The monograph was published by the Bayer Pharma publication fund of the Cape Town Post Graduate Medical Association. The work is recommended for all medical libraries.

*Nursing in Modern Society.* By Mary Ella Chayer, R.N. M.A. associate professor of nursing education. Teachers College, Columbia University. 8°, cloth 288 pp. New York: G. P. Putnam's Sons 1947 \$4.00.

This book has been written primarily for nurses, teachers and supervisors. The various current problems of nursing are discussed by the author in the following divisions: the impact of social forces upon nursing, the influence of social forces upon community health needs and building a better future for the nursing profession. Miss Chayer has called attention to the changing needs of society and to the changes that have already taken place in the nursing profession. The last chapter summarizes the twelve cardinal principles of professional service. The text is well written in an easy style and the material is well organized. The type paper and printing are excellent. A list of references and one of questions for study are appended to each chapter. A comprehensive general bibliography and a good index conclude the volume. The work should prove useful as a reference work to schools of nursing and as a textbook for postgraduate students. It is recommended for the reference collections of all medical libraries.

*Benjamin Silliman, 1779-1864. Pathfinder in American Science.* By John F. Fulton, M.D. and Elizabeth H. Thomsen. 8°, cloth, 294 pp. with seventeen illustrations. New York: Henry Schuman, 1947 \$4.00.

Benjamin Silliman is of interest to the medical historian because of the responsible part he took in organizing Yale University School of Medicine in 1813. He was eminent as a chemist and geologist and as a teacher of science. He established the great Peabody Museum of natural history and founded the first gallery of fine arts in an American academic institution, the Trumbull Gallery of Yale College. He was also largely instrumental in founding the Sheffield Scientific School, first called the School of Applied Chemistry. The authors of this well written biography for the general reader cover the professional life of Silliman from the time he was appointed professor of chemistry at Yale in 1802 until his retirement in 1853. The story is told in an easy narrative style. The book is well published and should be in all medical and scientific historical collections. It is one of a series in *The Life of Science Library*.

*400 Years of a Doctor's Life.* Collected and arranged by George Rosen M.D. and Beate Caspari-Rosen M.D. 8°, cloth, 429 pp. New York: Henry Schuman 1947 \$5.00.

This interesting anthology is made up of excerpts taken from formal autobiographies, letters and other writings of physicians, dead and living of the past four hundred years. The material is arranged according to epochs and incidents in a doctor's life: early years, school days, medical student days, the practice of medicine, scientist, scholar and teacher, the doctor marries, the doctor as a patient, the doctor goes to war, writing and politics and reflections on life and death. The selections are preceded by short biographic notes or comments. The absence of direct references to the sources of the selections will be deemed by the historian and bibliographer. A number of physicians appear more than once in different sections of the text and there should have

been an index in names to make the book useful as a reference work. The type, printing and paper are excellent. This unusual historical book should be in all collections of medical and general history.

*Calcium and Phosphorus in Foods and Nutrition.* By Henry C. Sherman Ph.D., Mitchell Professor of Chemistry, Rutgers University. 8°, cloth 176 pp., with seven figures and twelve tables. New York: Columbia University Press, 1947 \$2.75.

This semipopular monograph presents in plain language a summary of the place of calcium and phosphorus in present day nutrition. The first chapter discusses the role of calcium and phosphorus in nature in agriculture and in human nutrition. The following chapters deal with calcium in the body, the effects of food and growth upon the calcium content, chemical forms and nutritional functions of phosphorus, calcium and phosphorus requirements and the problem of necessary and optimal intakes and foods as a factor in the nutritional provision of calcium and phosphorus. An extensive bibliography of forty four pages is appended to the text. A good index concludes the volume. The text is well written in a pleasing style and the material is well organized. The publishing is excellent. The printing is well done with a good type on a good light paper. The volume is recommended for all medical and general libraries and to all persons interested in the subject.

*Surgical Disorders of the Chest. Diagnosis and treatment.* By J. K. Donaldson M.D. associate professor of surgery and in charge of thoracic surgery, University of Arkansas School of Medicine and member of surgical staff, St. Vincent's Infirmary and visiting staff, Baptist Hospital, Little Rock, Arkansas. Second edition thoroughly revised. 8°, cloth, 485 pp. with 146 illustrations and 2 color plates. Philadelphia: Lea and Febiger 1947 \$8.50.

This new edition of a standard treatise has been revised to include the knowledge gained during World War II. Decontamination of the lung is discussed in some detail. Selected references are appended in each chapter, and a good index concludes the volume. The publishing is excellent in every way. The book is recommended for all medical libraries and to surgeons interested in the subject.

*Principles of Occupational Therapy.* Edited by Helen S. Willard A.B. O.T.R. director, Philadelphia School of Occupational Therapy and Clare S. Spackman S.M. in Ed., O.T.R. director, curative workshop, Philadelphia School of Occupational Therapy, director, Occupational Therapy Department, Hospital of the Graduate School of Medicine, University of Pennsylvania, and assistant director, Philadelphia School of Occupational Therapy. 8°, cloth 416 pp. with 46 illustrations. Philadelphia: J. B. Lippincott Company 1947 \$4.50.

This new textbook is the joint work of twenty specialists in the field of occupational therapy. The text is divided into two sections: basic concepts and applied principles. The first section deals with the history, development, scope, educational aims and activities of the subject, and factors in the organization of occupational therapy departments. The second section discusses the place of the therapy in general and special hospitals with a chapter on children's hospitals and pediatric services and in United States Army and Navy hospitals during World War II. In this section there are chapters on the use of occupational therapy for patients with mental disease and tuberculosis, the visually handicapped and for patients with physical injuries. The last chapter of over a hundred pages is subdivided into three sections, dealing with treatment for limitation of motion of joints, flaccid paralysis and industrial injuries, for patients afflicted with cerebral palsy and for arthritic patients. The treatment is given in detail. The concluding chapter describes the rehabilitation program of the Veterans Administration. The work constitutes a treatise on the philosophy and practice of the subject. The text is well written, and the organization of the material is good. The volume is well published. The type is good and legible, and the printing on a soft light paper pleasing to the eye, is excellent. The book should be in all medical libraries and should prove valuable to all persons interested in physical therapy.



*A Text-Book of Mental Deficiency (Amentia)* By A F Tredgold, M D, F R C P, F R S (Ed), consulting physician to University College Hospital, London Seventh edition 8°, cloth, 534 pp., with 47 plates and 9 tables Baltimore Williams and Wilkins Company, 1947 \$8 50

This new edition of a standard textbook, last revised in 1937, has been brought up to date by the addition of considerable material Some chapters have been rewritten, and the changes made by the British Education Act of 1944 relating to educationally subnormal and defective children have been incorporated in the chapter on English law concerning mental defectives A good index concludes the volume The text, printed in Great Britain, is well done with a good type on good paper The book is recommended for all medical libraries and to all persons interested in the subject

## NOTICES

### ANNOUNCEMENT

Dr Franklin G Balch, Jr, announces the removal of his office to 1180 Beacon Street, Brookline, for the practice of general surgery

### SUFFOLK DISTRICT MEDICAL SOCIETY

The Suffolk District Medical Society will meet in Sprague Hall, Boston Medical Library, 8 Fenway, Boston, on Tuesday, May 4 The councilors will meet at 3 30 p m, and the annual meeting will be held at 5 00 p m

### MASSACHUSETTS SOCIETY FOR SOCIAL HYGIENE

The annual meeting of the Massachusetts Society for Social Hygiene will be held at a dinner at the Boston City Club, 14 Somerset Street, Boston, on Wednesday, April 28, 6 00 p m *Guest speaker* Dr Raymond A Vonderlehr of Atlanta, Georgia, medical director, Communicable Disease Center, United States Public Health Service, will speak on the subject "Past, Present and Future Responsibilities of the Social Hygiene Societies in the Control of the Venereal Diseases" Dr William A Hinton, chief of the Wassermann Laboratory, State Department of Public Health, and chief of the Laboratory Division of the Boston Dispensary, will be another guest of honor at the dinner Dr George Gilbert Smith will preside

The public is cordially invited to attend For details regarding the program, reservations for the dinner and so forth, application should be made in writing or by telephone to the office of the Massachusetts Society for Social Hygiene, 1145 Little Building, HANcock 6-3176

### NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the auditorium, Boston University School of Medicine, 80 East Concord Street, Boston, on Monday, April 26, at 8 15 p m Dr James M Faulkner will preside

#### PROGRAM

Diphtheritic Myocarditis Drs Norman H Boyer and Louis Weinstein

Clinical and Laboratory Features of First Attacks of Rheumatic Fever Occurring in Scarlet-Fever Patients Treated with Penicillin Drs Louis Weinstein, Louis Bachrach and Norman H Boyer

Acceleration of Flow in the Veins of Human Limbs by the Local Application of Pressure Drs Joseph R Stanton, Edward D Freis and Robert W Wilkins

Some Observations Concerning the Effect of Sympathectomy on the Human Heart Rate Drs Reginald H Smithwick, Earle M Chapman, Dera Kinsey and George P Whitelaw

The Effects of Veratrum Viride in Hypertensive Man Drs Edward D Freis, Joseph R Stanton, James W Culbertson, Julius Litter and Meyer H Halperin

Interested physicians and medical students are cordially invited to attend

### NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular meeting of the New England Society of Physical Medicine will be held at the Ring Sanatorium and Hospital, Arlington, Massachusetts, on Wednesday, April 21, at 8 p m Dr Volta R Hall will speak on the topic "Physical Medicine in the Treatment of Psychiatric Conditions"

Members of the medical profession are cordially invited

### AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION

The annual meeting of the American Clinical and Climatological Association will be held at White Sulphur Springs, West Virginia, from November 1 to 3 (secretary, James Bordley, III, M D, Mary Imogene Bassett Hospital, Cooperstown, New York)

### AMERICAN CONGRESS OF PHYSICAL MEDICINE

The twenty-sixth annual scientific and clinical session of the American Congress of Physical Medicine will be held from September 7 to 11, inclusive, at the Hotel Statler, Washington, D C Scientific and clinical sessions open to members of the medical profession in good standing with the American Medical Association will be given

Full information may be obtained by application to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois

### AMERICAN NEUROLOGICAL ASSOCIATION

The annual meeting of the American Neurological Association will be held in Atlantic City, New Jersey, from June 14 to 16, with headquarters at the Claridge Hotel (secretary-treasurer, H Houston Merritt, M D, Montefiore Hospital, Gun Hill Road, New York 67, New York)

### AMERICAN SOCIETY OF ANESTHESIOLOGISTS INC

A joint meeting of the American Society of Anesthesiologists, Inc, and the Western Divisions of the Canadian Anaesthetists' Society will be held at the Hotel Saskatchewan, Regina, Saskatchewan, Canada, on April 23 and 24

Physicians and medical students are invited

### MAINE MEDICAL ASSOCIATION

The annual meeting of the Maine Medical Association will be held in Poland Spring from June 20 to 22 (secretary, Frederick R Carter, M D, 142 High Street, Portland 3, Maine)

### MINNESOTA STATE MEDICAL ASSOCIATION

The annual meeting of the Minnesota State Medical Association will be held in Minneapolis from June 7 to 9 (secretary, B B Souster, M D, Lowry Medical Arts Building, St Paul 2, Minnesota)

### MONTANA STATE MEDICAL ASSOCIATION

The annual meeting of the Montana State Medical Association will be held in Billings on June 18 and 19 (secretary, H T Caraway, M D, 115 North 28th Street, Billings, Montana)

### NEW MEXICO MEDICAL SOCIETY

The annual meeting of the New Mexico Medical Society will be held in Las Vegas from June 3 to 5 (secretary, H L January, M D, 221 West Central Avenue, Albuquerque, New Mexico)

(Notices concluded on page xiii)

## NOTICES (Concluded from page 582)

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 22

## FRIDAY, APRIL 23

- \*9:00-10:00 a.m. Relief of Pain by Neurosurgical Procedures. Dr. William H. Sweet. Joseph H. Pratt Diagnostic Hospital.  
 \*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

## MONDAY, APRIL 26

- \*12:00 p.m. Clinicopathological Conference. Margaret Jewett Hall. Mt. Auburn Hospital. Cambridge.  
 \*8 p.m. New England Heart Association. Auditorium Boston University School of Medicine.

## TUESDAY, APRIL 27

- \*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.  
 \*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

## WEDNESDAY, APRIL 28

- \*9:00-10:00 a.m. Newer Concepts of Muscle Contraction. Dr. Gerhard Schmidt. Joseph H. Pratt Diagnostic Hospital.  
 \*12:00 p.m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.  
 \*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater. Children's Hospital.  
 \*6:00 p.m. Massachusetts Society for Social Hygiene. Boston City Club.

\*Open to the medical profession

- APRIL 19-23. American College of Physicians. Page 491, issue of J. by 31  
 APRIL 20. Greater Boston Medical Society. Page 543, issue of April 8  
 APRIL 20. South End Medical Club. Page 543, issue of April 8  
 APRIL 21. New England Society of Physical Medicine. Page 582  
 APRIL 23 and 24. American Society of Anesthesiologists, Inc. Page 582  
 APRIL 26. New England Heart Association. Page 582  
 APRIL 26-29. American Dermatological Association. Page 456, issue of March 25  
 APRIL 28. Massachusetts Society for Social Hygiene. Page 582  
 APRIL 29-May 2. American Academy of Pediatrics. Page 240, issue of February 12  
 APRIL 30 and MAY 1. American Gastro-Enterological Association. Page 456, issue of March 25  
 MAY 1. Suffolk District Medical Society. Page 543, issue of April 8  
 MAY 1. American Society for Clinical Investigation. Page 456, issue of March 25  
 MAY 3 and 4. Association of American Physicians. Page 492, issue of April 1  
 MAY 4. Suffolk District Medical Society. Annual Meeting. Page 582  
 MAY 4 and 5. Association of Military Surgeons of the United States. Page 456, issue of March 25  
 MAY 6. Suffolk Censors Meeting. Page 344, issue of March 4  
 MAY 6-8. American Association for the Study of Gonorrhea. Page 491, issue of July 31  
 MAY 9-14. American Psychiatric Association. Page 492, issue of April 1  
 MAY 11. Harvard Medical Society. Amphitheater of Building D. Harvard Medical School. 9:00 p.m.  
 MAY 12-14. Association of American Society of Genito-Urinary Surgeons. Skystop Lodge Skystop, Pennsylvania.  
 MAY 13. Indications for the Use of Forceps. Dr. Roy J. H. Serrano. Parvaneh Association of Physicians. 8:30 p.m. Haverhill.  
 MAY 16-22. American Board of Obstetrics and Gynecology, Inc. Page 344, issue of March 4  
 MAY 16-23. International College of Surgeons. Page 136, issue of January 22  
 MAY 17-19. American Ophthalmological Society. Page 492, issue of April 1  
 MAY 17-20. American Urological Association. Hotel Statler Boston  
 MAY 17-20. Association for the Study of Internal Secretions. Page 492, issue of April 1  
 MAY 18-22. American Association on Mental Deficiency. Copley Plaza Hotel, Boston  
 MAY 20-23. American Board of Ophthalmology. Page 170, issue of January 29  
 MAY 23-28. American Physiotherapy Association. Page 543, issue of April 8  
 MAY 24-26. American Gynecological Society. Page 543, issue of April 8  
 MAY 23-27. Massachusetts Medical Society. Annual Meeting. Hotel Statler Boston  
 MAY 27-29. American Surgical Association. Page 455, issue of March 25  
 JUNE 7-10. National Gastroenterological Association. Page 455, issue of March 25  
 JUNE 14-16. American Neurological Association. Page 582  
 JUNE 17-20. American College of Chest Physicians. Page 455, issue of March 25  
 JUNE 20 and 21. American Radium Society. Page 543, issue of April 8  
 JUNE 21 and 22. American Society for the Study of Sterility. Page 384, issue of March 11

- JUNE 25 and 26. Christian Medical Society. Page 492, issue of April 1  
 JUNE 28-30. American Academy of Pediatrics. Hotel Schroeder. Milwaukee Wisconsin  
 JULY 6-24. Students International Clinical Congress. Page 455, issue of March 25  
 JULY 12-17. First International Polymyositis Conference. Page 36, issue of January 1  
 AUGUST 11-21. International Congress on Mental Health. Page 344, issue of March 4  
 AUGUST 23-26. International Society of Hematology. Page 419, issue of March 18  
 AUGUST 26-28. American Association of Blood Banks. Page 420, issue of March 18  
 SEPTEMBER 7-11. American Congress of Physical Medicine. Page 582  
 SEPTEMBER 13-15. American Academy of Pediatrics. Olympic Hotel. Seattle Washington  
 SEPTEMBER 20-23. American Hospital Association. Page 310, issue of February 26  
 SEPTEMBER 29. Mississippi Valley Medical Editors Association. Page 170, issue of January 29  
 OCTOBER 6-9. American Board of Ophthalmology. Page 170, issue of January 29  
 NOVEMBER 1-3. American Clinical and Climatological Association. Page 582  
 NOVEMBER 8-12. American Public Health Association. Page 420, issue of March 18  
 NOVEMBER 20-23. American Academy of Pediatrics. Annual Meeting. Capital Madison Hall Hotel, Atlantic City New Jersey  
 DECEMBER 7-9. Southern Surgical Association. Annual Meeting. Page 543, issue of April 8

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

- MAY 11. Annual Meeting. Hotel Walden Greenfield.

## MIDDLESEX EAST

- MAY 12. Annual Meeting. 6:45 p.m. Beer Hill Golf Club Wakefield

## PLYMOUTH

- MAY 20. Lakeside Sanatorium. Lakeside.

## SUFFOLK

- MAY 1. Spring Dinner  
 MAY 4. Annual Meeting  
 MAY 6. Censors Meeting

## WORCESTER

- MAY 12. Annual Meeting

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## CARCINOMA OF THE STOMACH\*

CLAUDE E. WELCH, M.D.,† AND ARTHUR W. ALLEN, M.D.‡

BOSTON

**S**URGICAL experience with carcinoma of the stomach at the Massachusetts General Hospital has been reviewed by Parsons<sup>1</sup> in previous papers covering the years 1922 to 1926, and the period from 1927 to 1936 by Parsons and Welch.<sup>2</sup> This report includes all patients admitted to this hospital on whom the diagnosis was made during the ten-year period 1937 to 1946 inclusive.

In the compilation of these figures, it is, of course, our hope to show that increased knowledge of the disease and its amenability to surgical attack have resulted in a steadily increasing five-year salvage rate. But it is of equal importance to consider the trends in management of patients with cancer of the stomach. In this brief summary, only our own experience can be considered, and no attempt is made to cover the voluminous literature comprehensively.

Several methods can be listed by means of which the curability rate can be increased. They are as follows: earlier diagnosis, that more patients with carcinoma will arrive in the hospital in a curable stage, more radical approach to the problem of gastric ulcer, that a certain number of cancers masquerading as ulcers will not be overlooked, extension of the type of operation so that by a wider excision of involved tissue, more cures may be obtained, and a reduction in the postoperative mortality, so that cases favorable for cure are not lost.

### DELAY BEFORE TREATMENT

Theoretically, if all patients were subjected to resection as soon as carcinoma of the stomach developed, all would be cured. Early diagnosis is therefore of the utmost importance. A vivid illustration of this point is furnished by the following case.

F. C. (M.G.H. 61931) a 58-year-old man, entered the hospital on June 27, 1934, because he had vomited blood three times in the previous month. X-ray studies, including

an upper gastrointestinal series were negative. Gastroscopy showed chronic gastritis. Because of the possibility of carcinoma of the stomach, exploratory operation was performed. A 2-cm lymph node found on the greater curvature, on frozen section showed highly malignant carcinoma. Because metastasis was already present, the surgeon did only a local excision of a small carcinoma of the greater curvature, and did not remove any other lymph nodes. The pathological report was adenocarcinoma. The patient was living and well 12 years later. Despite the high malignancy of the tumor and an inadequate operation, early surgery effected a cure.

Cancer of the stomach, once established, is usually a very rapidly growing tumor. This is shown by the rarity of cancers of the stomach discovered incidentally at post-mortem examination, when death is due to some other cause. This behavior is in contrast to that of carcinoma of the prostate, which is not uncommonly discovered in autopsy specimens as an incidental finding.

This behavior of carcinoma of the stomach has been recognized for many decades, and a vast amount of educational information has been spread by various cancer-control groups in an effort to bring the patient with gastric symptoms to the surgeon in time for cure. At the same time, the medical profession has become more alert to the problem, and early diagnosis has been facilitated by better x-ray films and an increased use of the gastroscopy.

It seemed probable, therefore, that a comparison of the delay before treatment would show a significant decrease in this last decade. To obtain comparable series, the length of time that elapsed from the onset of gastric symptoms to the date that the patient entered the hospital for treatment was determined for all patients undergoing operation during the twenty-year period 1927 to 1946. The delay in the first ten-year period was then contrasted with that in the latter (Fig. 1). The remarkable and unhappy result is that the two curves can be almost exactly superimposed.

Why does the average delay before treatment still remain at the high level of five months? Is it apathy on the part of the patient or neglect by the physician? One is inclined to believe that all

\*Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 3, 1947.

†Instructor in surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.

‡Attending in surgery, Harvard Medical School; chief, East Surgical Service, Massachusetts General Hospital.

educational efforts have been negated by the radio and advertising columns with their promises of "relief for acid indigestion." Perhaps the medical profession should be satisfied that it is not fighting a losing battle against this propaganda, and conclude that if the public wishes to be cured of cancer of the stomach, it had better do something to aid itself.

No special attempt has been made in this study to discover the length of life of the untreated cases. It has been shown by Nathanson and Welch<sup>3</sup> and by Livingston and Pack<sup>4</sup> that the average duration

Allen and Welch,<sup>6</sup> in a review of gastric ulcers observed at the Massachusetts General Hospital from the years 1931-1940, found that 14 per cent of ulcers first considered to be benign were later proved to be malignant. No certain method could be found to differentiate the two types of lesions, but some conclusions were drawn that serve as a guide in therapy.

Immediate surgery is recommended in patients with a gastric ulceration under any one of the following conditions: if the ulcer is of short duration and the patient is over fifty years of age, if the ulcer is over 2.5 cm. in diameter, if there is no free hydrochloric acid in the stomach, if the ulcer is in the greater curvature or on the prepyloric region, and if the ulcer is chronic or recurrent and on the lesser curvature. Hospital observation and medical treatment for one month are advised if the lesion is acute and in a young patient, is under 1 cm. in diameter and is in the lesser curvature or on the anterior or posterior wall. If, in the last group, healing is not complete in a month, surgery is advised.

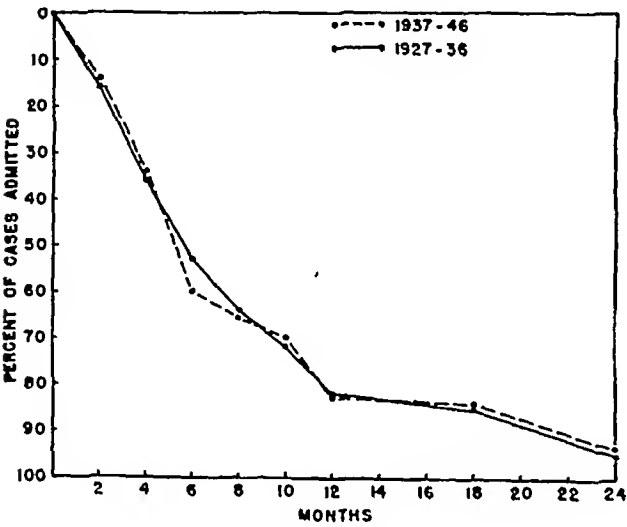


FIGURE 1 Delay in Seeking Treatment among All Cases of Cancer of the Stomach in Which Operation Was Performed. The duration of symptoms before hospital admission is divided into ten-year periods.

of life is about a year from onset of symptoms, and that 90 per cent of all patients are dead at the end of two years. The average delay from onset of symptoms to hospital entry of patients not subjected to surgery in the present series was about six months, at that time, operation was judged unwise or was refused by the patient.

Once the patient has been admitted to the hospital, he is studied completely. Endoscopy, as Benedict<sup>5</sup> has shown, is of great value, especially with lesions high in the stomach, since esophageal involvement may be observed. Peritoneoscopy is often valuable, especially if the patient has no symptoms of obstruction. If hepatic or peritoneal metastases are found, in the absence of obstruction, an operative procedure is contraindicated. On the other hand, if obstruction is present, the exploration is nearly always recommended, even if metastases are present, in the hope that a short-circuit may make the patient's life more comfortable.

The therapeutic procedures employed in the various periods are listed in Table 1.

THE PROBLEM OF GASTRIC ULCER

The well known fact that gastric cancer frequently simulates benign gastric ulcer needs re-emphasis.

TABLE 1 Types of Therapy Employed in All Cases of Carcinoma of the Stomach

PERIOD	TOTAL NO OF CASES	NO OPERATION	LAPAROTOMY ONLY	PALLIATIVE OPERATION	RESECTION
		NO OF CASES	NO OF CASES	NO OF CASES	NO OF CASES
1927-1931	296	115	55	58	68
1932-1936	395	135	88	69	103
1937-1941	375	95	73	36	171
1942-1946	457	105	85	22	245

able, if healing is complete, repeat observation should be made one month after discharge from the hospital.

Another method of determining the diagnosis is by means of the cytologic smear, according to Papanicolaou's<sup>7</sup> technic. Fresh gastric washings are precipitated and stained. If malignant cells are found, the diagnosis is almost surely carcinoma. On the other hand, with known cancer of the stomach, the smear will be positive in only about two thirds of the cases. Thus, in the Vincent Memorial laboratory, the results to date have been as follows: in 50 cases of gastric ulcer or cancer in which gastric smears were employed, 24 patients proved to have carcinoma of the stomach, and the smears were positive in 15, of 26 patients without cancer, the smear was reported positive in 1, who proved to have a benign ulcer.<sup>8</sup>

If these recommendations are followed, there will be no significant delay in the recognition of gastric cancers. Furthermore, the very rare case of cancer that will "heal" under the best medical therapy (we have had at least 2 cases in this hospital) will soon be discovered, for the ulceration will recur after the patient leaves the hospital.

That the differential diagnosis of ulcer and cancer is still difficult is attested by the fact that 11 per cent of all the resections in the patients in the present study were made with the preoperative diagnosis of benign gastric ulcer. Fortunately, the delay before operation has been diminished in this group, because it has become appreciated that gastric resection for gastric ulcer produces excellent results, as shown by St. John et al.<sup>9</sup> and Judd and Priestley.<sup>10</sup>

One may ask how many lives might be saved if all the gastric carcinomas in this group were recognized and surgery performed at an early date. Since about 25 patients with apparent gastric ulcer appear in a year in this hospital, of whom about 14 per cent have carcinomas, 3 or 4 patients will be subjected to an earlier resection. Since the five-year curability rate is at least 40 per cent in this group, at least one additional cure a year should be expected in this hospital by early resection. But it is imperative for the surgeon to realize that, even when he has the stomach in his hands, he cannot make the differential diagnosis between ulcer and cancer, and that he must carry out the proper operation for gastric cancer.

#### EXTENSION OF THE OPERATIVE PROCEDURE

Gastric resection for carcinoma originally involved no attempt to excise any tissue but that of the stomach itself. However, the importance of removal of the regional lymph nodes along the lesser and greater curvatures was soon recognized, since the earliest metastases are usually found there. A second feature was emphasized by Castleman,<sup>11</sup> who showed the frequency of invasion of the proximal centimeter of duodenum by cancer of the stomach; he found that extension rarely proceeded beyond this level. A third site of early extension pointed out by Ogilvie<sup>12</sup> and Allen<sup>13</sup> is the great omentum. Metastases there are not uncommon, and may be overlooked except on microscopic section.

These three areas — the regional lymph nodes, the proximal centimeter of duodenum and the great omentum — should be removed with every resection for cancer of the stomach in which cure is the objective. Of course, if disease is to be left behind in other spots inaccessible to surgical removal, and only a palliative resection is planned, there is no need to remove the omentum in every case, although it is usually better to do so. After a long experience with this procedure, we are convinced that it carries no hazard and may contribute to a smoother convalescence.

As a corollary to the concept that gastric ulcer should be considered to be cancer until the pathologist proves it to be benign, it follows that the same operation should be carried out for gastric ulcer as for gastric cancer — that is, the removal of regional lymph nodes, great omentum and proximal duodenum. There is nothing more distressing to the surgeon than to read the pathologist's report

"carcinoma of the stomach, no lymph nodes are included with the specimen." Yet this happens all too frequently, and many patients who should have the best chances of cure are doomed because of an inadequate operation.

Proximal extension of carcinoma of the stomach to the cardia often requires the procedure of total gastrectomy. This operation, although mentioned in the previous report, was a surgical rarity at that time. The technic as subsequently developed and described by Allen<sup>13</sup> has been followed in this hospital. Since the patients subjected to the procedure usually have extensive tumors, the mortality rate is bound to be high, and the number of cures small. The postoperative life span, however, is often surprisingly long.

The operation of total gastrectomy, in addition to an increased postoperative mortality, has other undesirable features. After operation, it is difficult for many patients to maintain adequate nutrition, and an anemia of significant grade is not uncommon. Studies of patients who have had recurrence after subtotal resections for cancer usually show that metastatic involvement of lymph nodes is present but that the remaining stomach is uninvolved. For these reasons, we do not subscribe to Longmire's<sup>14</sup> theory that all patients with carcinoma of the stomach should be treated by total gastrectomy.

The operative attack on carcinoma of the stomach, has, in the past, been limited by inaccessible proximal extension of the growth into the esophagus and mediastinum. Although it was frequently possible to draw down 3 to 5 cm. of the esophagus and do a total abdominal gastrectomy, in many cases it was impossible to get an adequate margin above the tumor. Recently, Churchill<sup>15</sup> and Sweet,<sup>16</sup> in pioneer work in this hospital, have developed the technic of transthoracic gastrectomy. With this approach through the diaphragm, extension of the cancer into the esophagus is easily amenable to resection.

There are several organs that can be sacrificed, resection en bloc with the carcinoma of the stomach being used. Thus, the transverse colon, the pancreas, the spleen and rarely a local extension into the liver can be resected with the tumor. It is our experience that none of these patients will survive five years, but recurrence of the disease will be delayed.

There are, unfortunately, many areas of metastasis that cannot be removed surgically. Metastatic lymph nodes in the head of the pancreas about the superior mesenteric artery or about the hepatic artery are nearly always nonresectable. Whereas a regional-lymph-node dissection of the left gastric artery may be done, a cure is not to be expected if the nodes about the celiac axis are involved. Metastatic lesions in the liver, if demonstrable, are indicative of widespread involvement of the organ. Removal of visible hepatic metastases will not con-

tribute to the postoperative comfort of the patient or increase the five-year survival rate. Peritoneal metastases are likewise indicative of widespread lymphatic involvement, local removal is useless.

The question might be asked regarding the relative importance of these extensions of the operative procedure so far as the control of cancer of the stomach is concerned. Five-year survivals are not to be expected if other viscera are involved as well as the stomach, so that massive resections of multiple viscera should be considered of value only as palliative procedures. On the other hand, there are rare

continued parenterally several days afterward. Sodium sulfadiazine was employed intravenously for some time before penicillin was available, and is still utilized in some cases. The sulfonamides cannot be used locally with safety, and, as a rule, they may be employed for only a short time because of the danger of renal complications.

Blood replacement has also played an important role. It is essential to remember that a normal red-cell count and hematocrit may be misleading in any given patient, since the blood volume may be low, as Lyons<sup>18</sup> has pointed out. Blood is now given

TABLE 2 Mortality with Various Types of Gastric Resection

TYPE OF OPERATION	NO. OF CASES		OPERATIVE DEATHS		OPERATIVE MORTALITY	
	1937-1941	1942-1946	1937-1941	1942-1946	1937-1941 %	1942-1946 %
Abdominal approach						
Subtotal palliative resection	35	32	13	2	37	6
Subtotal resection for cure	96	99	11	3	11	3
Total resection	35	34	17	11	49	32
Transthoracic approach						
Subtotal resection	4	48	2	2	50	4
Total resection	1	32	1	9	100	28
Totals	171	245	44	27		
Averages					26	11

five-year survivals after total gastrectomy. Obviously, the transthoracic approach has opened a new field that cannot yet be appraised accurately.

#### REDUCTION OF POSTOPERATIVE MORTALITY

The method of increasing the number of five-year cures of cancer of the stomach that has heretofore seemed to offer the most promise has been the reduction of excessive postoperative mortality. Thus, in the period 1932 to 1936, the mortality of gastric resection for cancer was 25 per cent. If these patients had not died, the five-year cures following resection would have increased by the same percentage.

It is gratifying to note that the mortality of resections has declined appreciably in recent years. The factors that have contributed are chiefly improved anesthesia, more careful blood, protein and vitamin replacement and chemotherapy. The anesthetic agent now employed is most commonly ether, by intratracheal administration, although our choice in patients who are not to have the diaphragm opened is continuous novocain administered in the spinal area by the method of Arrowood and Foldes.<sup>17</sup>

Local and parenteral use of penicillin just before, during and after operation has contributed a great deal to a smooth convalescence. Especially in transthoracic approaches, Sweet<sup>16</sup> has found that the use of penicillin has practically eliminated the complication of empyema. It appears to be no less effective in the peritoneal cavity. For full effect, it should be started before operation and

very liberally, therefore, despite normal laboratory figures. Likewise, intravenous amigen or amino acids and vitamins are administered in large doses when indicated preoperatively and as a routine measure postoperatively.

A technical contribution of great importance is that of Allen and Donaldson,<sup>19</sup> who introduced the routine use of double jejunostomy after gastric resections. The proximal tube is led back through the gastroenterostomy, and the distal one serves as a jejunostomy for feeding. Thus, the stomach is decompressed postoperatively without the use of a Levine tube. Stomal obstruction, which occurred in about 1 out of 20 patients in the series of Allen and Welch,<sup>20</sup> is no longer to be feared as a complication.

Although pulmonary emboli have not been eliminated as a cause of death, they have been reduced in number in recent years by prophylactic ligation of the superficial femoral veins, by the method of Allen, Linton and Donaldson.<sup>21</sup> We believe that this procedure is indicated in any patient who has a curable lesion, preferably at the time of resection, or within forty-eight hours thereafter.

These advances in therapy have resulted in a definite decrease in the number of postoperative deaths. Table 2 and Figure 2 show that the percentage of postoperative deaths has consistently diminished although the operability has increased.

To determine the effect of postoperative mortality on the curability rate, it is necessary to divide the resections into various groups (Table 2). Subtotal resections "for cure" represent cases in which the

surgeon has removed all gross cancer from the abdomen, and is the group that actually contains nearly all the cured patients. "Palliative" subtotal resections include cases in which cancer is left behind in inaccessible areas at the time of resection, no cures are to be expected. With total gastrectomies five-year cures are very rare, whereas trans-thoracic gastrectomies have not been done long enough to evaluate the curability rate. Hence, only subtotal resections for cure need be considered

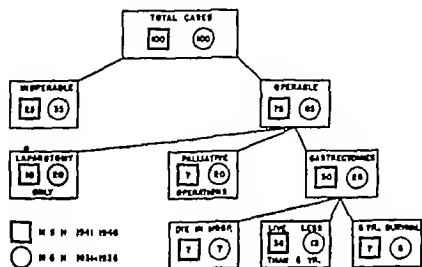


FIGURE 2. Prognosis in Cancer of the Stomach  
The fate of all patients entering the hospital with this diagnosis is demonstrated by decades

The postoperative mortality in this group was 11 per cent in 1937 to 1941, and 3 per cent from 1942 to 1946. This means that the factor of postoperative mortality can, at present, no longer be reduced significantly, and that other methods must be found to increase the number of cures.

#### FIVE-YEAR SURVIVALS

What, then, is the ultimate fate of the patient who enters the hospital with carcinoma of the stomach? A graphic summary, comparing the results of the present decade with those of the last, is given in Figure 2, in which the results from 1927 to 1936 are shown by the circled figures. The results in the present series are included in the heavy squares. Incidentally, it may be noted that, in the last five-year series in which it was possible to determine end-result so far as five-year cures are concerned (1937 to 1941), only 4 patients have been untraced. They are considered in the tables to be dead of disease. Several trends are immediately discernible: the number of apparently operable patients has risen from 65 per cent to a level of 75 per cent, the patients who have an operation are much more likely to have a gastrectomy than they were before (50 per cent of all cases, compared with 25 per cent), whereas the percentages of exploratory laparotomies remain about the same and those of palliative operations other than gastrectomy have decreased, in the cases of gastrectomy, there is

little change in the number of hospital deaths, and many more patients live up to four years after operation, and the over-all number of five-year cures has increased from about 5 per cent to 7 per cent.

It is clear that the great increase in the number of gastrectomies is due to the more widespread use of resection as the best palliative operation, even if all gross disease cannot be removed. The increased number of palliative resections has maintained the over-all mortality for resection at the same level as that of the previous study.

A further analysis of the gastrectomies performed is presented in Figure 3. There were no five-year survivals in the patients who had gross disease left in the abdomen, and only a rare five-year survival after total gastrectomy. Practically all the favorable cases fell into the group of subtotal resections, in which all gross cancer is removed.

The statement has sometimes been made that, even if gross cancer is left behind in the abdomen, a cure may result. Our information lends no credence to that claim. Eighty-five per cent of the patients with palliative subtotal gastrectomy were dead a year after operation, and all were dead two years after operation. The average postoperative length of life was about eight months.

Since the average length of life after exploratory laparotomy alone for cancer of the stomach is about six months, palliative gastric resections cannot be defended on the basis that a significant pro-

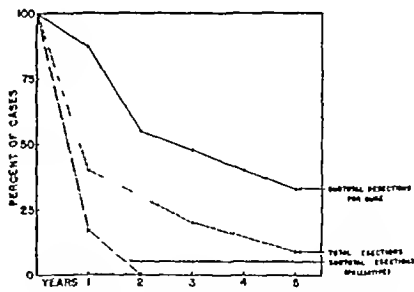


FIGURE 3. Duration of Life after Various Types of Gastric Resections for Cancer (1937-1941)

longation of life results. On the other hand, patients who have had an obstructing lesion removed are usually more comfortable and may die a relatively painless death from hepatic or pulmonary metastases. Since some patients without hope of cure are condemned to life for a period after operation, such a resection is really palliative. It seems justifiable to continue the use of the term "palliative gastrectomy" to distinguish operations in which gross disease is left behind in the abdomen.



Livingston and Pack<sup>4</sup> have used the term "resectable cancer of the stomach" to describe cases in which all gross cancer can be excised. This is a valuable term, and in the present study is represented by all the subtotal resections, total resections and those done by the transthoracic route in which all gross disease can be removed. In the present series, the mortality for "resectable cancer" is 19 per cent, and the five-year curability is 20 per cent.

The prognosis of any case of carcinoma of the stomach may be gauged fairly accurately by microscopical examination of the specimen. The presence of metastasis to the regional lymph nodes is very

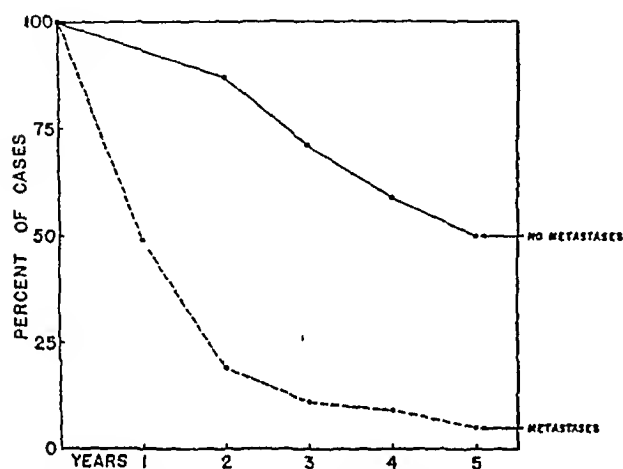


FIGURE 4 Metastasis and Postoperative Duration of Life after Gastric Resection for Cancer

The end-results of all survivals indicate the importance of metastases in the determination of prognosis

grave. Thus, in the years 1937 to 1941, there were 73 operative survivors who had metastases. Only 4 patients, or 5 per cent, lived five years. On the other hand, of the 42 patients who survived operation and had no extension to the regional nodes 20, or about 50 per cent, lived five years (Fig 4).

#### DISCUSSION

Livingston and Pack,<sup>4</sup> in their very complete survey of the treatment and end-results of gastric cancer, present many figures that are interesting to compare with this present series. It must be pointed out that their monograph was published in 1939 and that all clinics have improved their results since then. Thus, Pack<sup>22</sup> has recently reported that the operability in the Memorial Hospital has risen to 50 per cent. Therefore, no special credit need be taken by the Massachusetts General Hospital, except to point out that, here as well as elsewhere, modest gains have been registered in the therapy of cancer of the stomach.

Livingston and Pack state that there is no report in the literature in which the resectability was over 36.4 per cent and that the average rate was 18.7 per cent. Marshall and Welch,<sup>23</sup> in a recent report from the Lahey Clinic, found that 24.1 per cent of all patients with a diagnosis of cancer of the stomach in the years 1936 to 1940 had a resection. Somewhat similar figures were reported by Counsellor<sup>24</sup> from the Mayo Clinic, where resection is carried out in 30 per cent of the patients with a diagnosis of gastric cancer. In our series, 50 per cent had resections, in 16 per cent inaccessible gross disease was left behind, whereas in 34 per cent all gross cancer was excised. The high resectability in this group has contributed to a comparatively high over-all postoperative mortality — 22 per cent. However, during the last five years of the study, although the resectability has increased from 45 to 54 per cent, the postoperative mortality has been reduced to 11 per cent.

Livingston and Pack also found that the average rate of postoperative five-year survivals from surgical treatment in the clinics studied was less than 2 per cent of the patients observed, the best rate reported from any surgical clinic or cancer center has never exceeded 5.2 per cent. In this series, from the years 1937 to 1941 (the last period available for end-results), there were 7 per cent five-year survivals.\*

#### SUMMARY

A study of all the patients with carcinoma of the stomach admitted to the Massachusetts General Hospital during the ten-year period 1937 to 1946 shows that the delay before treatment has remained unchanged, averaging five months. A more aggressive attitude toward gastric ulcer has increased the recognition of early cancer of the stomach.

The introduction of a transthoracic approach and the wider use of total abdominal gastrectomy have increased the number of cases available for resection.

The mortality for gastric resections for cancer has dropped to a present level of 17 per cent for the entire series and to 11 per cent in the last five-year period. The mortality of subtotal resections in which all gross disease is removed has been 3 per cent in the last five-year period.

Meanwhile, the number of unoperated patients has declined so that 75 per cent have an operation. Fifty per cent of the total have a gastrectomy, either subtotal or total.

The best palliative operation, if gross disease cannot be removed, is subtotal gastrectomy.

The five-year survival rate is now 7 per cent of the entire group that enters the hospital.

The most fruitful method now available to increase the number of cures of cancer of the stomach

\*Since this article was submitted for publication, State, Moore and Wangenstein<sup>25</sup> have surveyed the patients with carcinoma of the stomach entering the University of Minnesota Hospital from 1936 to 1945. Their figures show a 55.2 per cent resectability, with a mortality of 16.6 per cent, and an over all five-year salvage of 6.6 per cent.

is to reduce the delay from onset of symptoms to surgical intervention

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## COMPLETE HEART BLOCK\*

### A Study of Two Cases in Veterans of World War II

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A NUMBER of reports in the medical literature emphasize the fact that some patients with complete heart block may have a favorable prognosis regarding life and the ability to perform daily tasks. In nearly every case the conduction defect is thought to be congenital in origin. Campbell,<sup>1</sup> in his discussion of congenital complete heart block, states that, "if there are no complications carrying special risks of their own, the prognosis is good and will probably prove that the condition is compatible with survival to old age." The cases reported below emphasize the ability of people affected with this malady to lead normal lives and at times to undergo rather strenuous exertion without demonstrable ill effects. Both patients were veterans of World War II. Only 1 case is reported in the literature in which a patient with complete heart block, apparently congenital in origin, was a member of the armed forces.<sup>1</sup>

## CASE REPORTS

**CASE 1** A 34-year-old man reported to the Out Patient Department on June 11, 1947, for compensation examination because of complete heart block. He had been inducted into the service on December 7, 1943. Preinduction physical examination had revealed a resting pulse rate of 34

rising to 80 on exercise. The remaining examination revealed no abnormalities. After induction he completed 8 weeks of basic training. During a routine screening examination a systolic apical murmur was heard and the patient

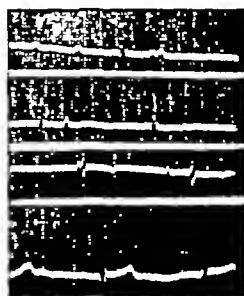


FIGURE 1. Tracing Obtained in Case 1 on May 15, 1943, Showing Complete Atrioventricular Dissociation with an Atrial Rate between 53 and 60 and a Ventricular Rate of 43. The T waves are upright in Lead I, diphasic in Lead 2 and inverted in Lead 3. The T waves in Lead IV are upright.

was hospitalized for observation. An electrocardiogram taken on May 15 had shown complete heart block with a diphasic T wave in Lead 1, inverted T waves in Leads 2 and 3 and an upright T wave in Lead 4 (Fig. 1). No other

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significant abnormality had been demonstrated during the study. The patient had been discharged from the service on June 5 and had subsequently been employed as a night clerk in a hotel, where he performed general manual labor.

The past history revealed a normal birth after a normal period of gestation. As a child the patient had measles, mumps, chicken pox and pertussis. At the age of 23, while playing baseball, he suddenly fainted. Since that time he had experienced six similar episodes, the last occurring at the age of 28 years. Additional medical history revealed that when the patient was 25 years old he had been told that he had a "bad heart." There was no history of scarlet fever, rheumatic fever, tuberculosis, syphilis or diabetes. The patient had attended school until he was 13 years old. At that time he completed the sixth grade, he incurred no difficulty in learning, but his schooling was stopped owing to the death of his father, whose position as a bread winner the patient accepted. At first he worked as a farm hand and later as a

Fluoroscopic examination of the heart showed the cardiac silhouette to be normal in size and shape.

An electrocardiogram revealed a complete heart block, with a diphasic T wave in Lead I and inverted T waves in Leads 2, 3 and F<sub>4</sub> (Fig. 2).

**CASE 2** A 19-year-old veteran reported to the Out-Patient Department for treatment because of "heart trouble" and "weakness."

The patient had been a premature baby and had supposedly weighed only 3 pounds at birth. A further developmental history did not reveal anything unusual. The patient had had measles, mumps, whooping cough and chicken pox. After the period of childhood, except for occasional sore throat, he had never been sick. There was no history of scarlet fever, rheumatic fever, tuberculosis, diphtheria or syphilis. He gave a history of two syncopal attacks, both occurring at the pre-school age. No details concerning these episodes

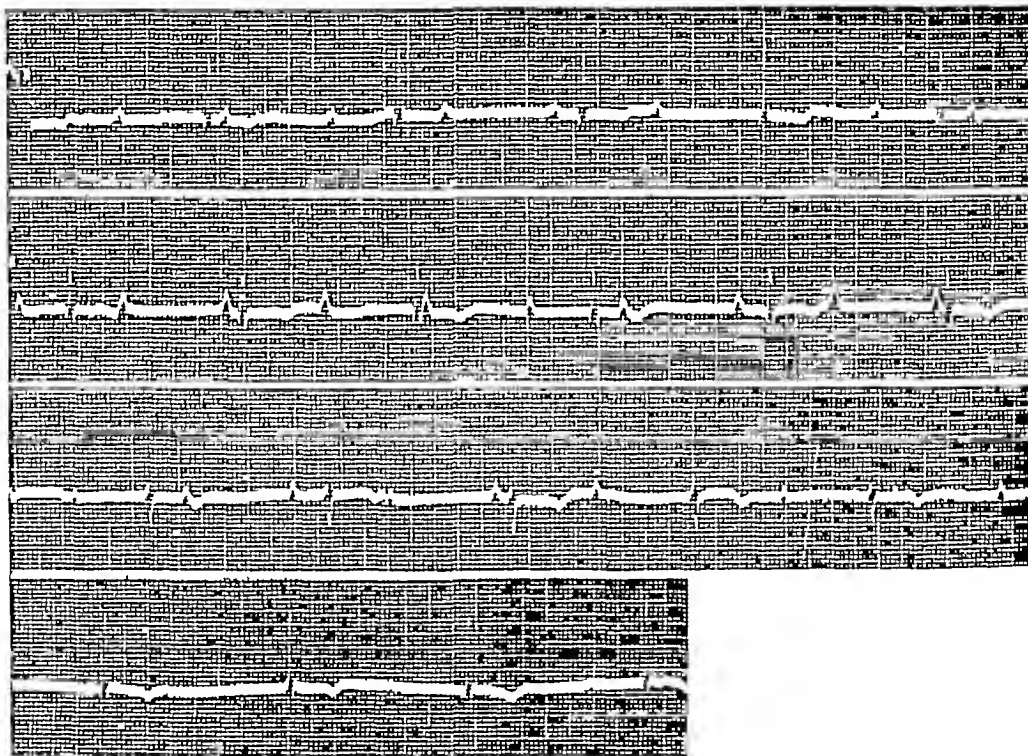


FIGURE 2 *Electrocardiogram Obtained in Case 1 on June 11, 1947, Showing Complete Heart Block. Note the T-wave changes that have taken place since the last observation.*

laborer on a railroad. He also held a job in a canning factory and finally was employed as a guard in a defense plant. He had no difficulty performing any of these tasks.

The family history was irrelevant.

Physical examination revealed a well developed and well nourished man who appeared to be in excellent health. The height was 69 inches, and the weight 175 pounds. An exercise-tolerance test, consisting of stepping on and off a chair 18 inches high twenty-five times, caused only a mild dyspnea. Examination of the heart showed no enlargement. There was a Grade I, blowing, systolic apical murmur transmitted only slightly toward the sternum. The murmur was somewhat accentuated by exercise. The remainder of the physical examination disclosed nothing of note.

The blood pressure was 120/80. The resting pulse was 52, rising to 80 after exercise.

Examination of the blood disclosed a red-cell count of 4,450,000 and a white-cell count of 6000, with 66 per cent neutrophils and 34 per cent lymphocytes. The sedimentation rate was 1 mm in 1 hour.

were obtainable. While in school he had no difficulty keeping up with other children. He was a member of the high-school basketball team. After completing 2 years of high-school education, he went to work for a packing company. This called for arduous manual labor, which he was able to perform without any ill effects. His next job was that of a truck driver. He subsequently passed a physical examination for a Civil Service position, which he held until his enlistment in the United States Navy on January 5, 1945. Physical examination performed prior to enlistment showed a pulse rate of 48, which increased to 56 with exercise. The remainder of the examination was reported as showing nothing of note. The patient was accepted for duty with the Navy and had no difficulty until April 25, 1945, when he reported to sick bay because of an upper respiratory infection. At the time of admission to the hospital the pulse rate was 44, "increasing only slightly with exercise." A diagnosis of complete heart block was made, the diagnosis being confirmed by a number of electrocardiographic tracings. The patient was discharged from the service on July 10 and subsequently re-

turned to his old job that of a truck driver. He was unable to perform his duties as well as he did before he entered the Navy because, as he put it, "he felt weak all over."

The family history was of no consequence.

Physical examination disclosed a patient of hyposthenic habits. He did not appear either acutely or chronically ill. An exercise tolerance test consisting of stepping on and off a chair 18 inches high revealed only a mild dyspnea. Examination of the heart disclosed some enlargement to the left, the left border of cardiac dullness being slightly outside the midclavicular line. No thrills were palpable either

rate as compared with acquired complete heart block. The study of the 2 subjects revealed some evidence that may justifiably be construed as indicative of disease of the heart other than the conduction defect. In Case 1 there was an associated progressive inversion of the T waves in Leads 1, 2, 3 and F<sub>4</sub>. This may have been due to some obscure pathologic process, possibly infectious in origin, in-

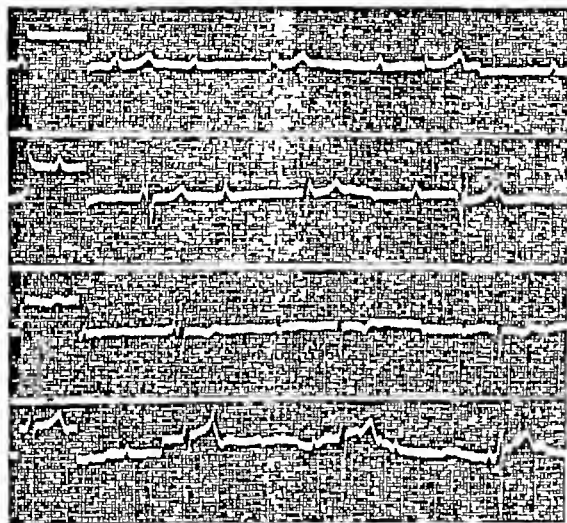


FIGURE 3. *Electrocardiogram in Case 2 Showing Complete Heart Block with an Atrial Rate of Approximately 60 and a 1:1 Ventricular Rate of 33.3. No other significant abnormalities are noted.*

before or after exercise. There was a Grade II blowing systolic murmur, which was best heard in the third and fourth interspaces just to the left of the sternum. This murmur was transmitted toward the apex and was somewhat accentuated by exercise. The remainder of the examination was negative.

The pulse rate was 40, regularly increasing to 52 with exercise. The blood pressure was 140/70.

Fluoroscope examination showed a mild enlargement of both the right and left ventricles.

An electrocardiogram revealed a complete heart block (Fig. 3).

### DISCUSSION

It is true that the etiology of the heart block in the cases reported above is open to question. However, the following findings strongly suggested the congenital origin of the conduction defect: the absence of an acquired etiologic agent that is known to affect the myocardium, the ability of the patients to lead normal lives and at times to undergo rather strenuous exertion without demonstrable ill effects, and the presence of a relatively faster pulse

volving the myocardium or the pericardium, or both, or to a process involving the coronary arteries. No definite conclusion can be reached at present. In Case 2 the systolic murmur coupled with the enlargement of the heart might perhaps be ascribed to the increased stroke volume associated with the slow heart rate.

A review of the literature regarding congenital complete heart block showed a lack of uniform criteria to which a case must conform before it may be assumed to be congenital in origin. Yater,<sup>2</sup> in a review of this subject in 1929, pointed out certain requirements that should be fulfilled before a diagnosis of congenital complete heart block can be made. These are as follows: electrocardiographic proof of heart block, a record of a slow pulse at an early age, and absence of a history of infection, especially diphtheria, rheumatic fever, chorea or congenital syphilis. He also stated that syncopal

attacks at a fairly early age and the presence of other congenital heart lesions add weight to the congenital etiology of the heart block. Most writers assume that complete heart block in children and young adults is to be considered infectious in origin until proved otherwise. Recently, different ideas were expressed.<sup>1, 3</sup> Leys<sup>4</sup> points out that permanent complete heart block following infection is rare and also states that the burden of proof lies on the shoulders of the one who assumes that a case of complete heart block in young adults is due to infection. White<sup>5</sup> asserts that permanent heart block following an acute infectious process is rare and that the most frequent cause of complete heart block is coronary-artery disease. Campbell,<sup>6</sup> in a review of 64 cases of complete heart block, found that 13 per cent were congenital in origin, and slightly over 10 per cent could be accounted for by syphilis and rheumatic fever. Seventy-five per cent of the cases were due to coronary-artery disease.

Subjective complaints caused by congenital complete heart block are few. A small percentage of the patients experience Stokes-Adams attacks or shortness of breath, or both, on moderate exertion. Others develop neurasthenia after learning about their malady.

Yater<sup>2</sup> calls attention to the relative infrequency of cyanosis in these patients. When cyanosis is found, it is probably due to an accompanying heart lesion rather than to the heart block per se. Physical examination usually reveals a pulse rate of 40 to 50 and an enlarged heart. This cardiac enlargement may be attributed to an associated heart lesion or to prolonged diastolic filling due to slow heart rate.

It is of great practical importance to differentiate congenital complete heart block from the acquired condition, for the prognosis for life and the capacity to lead normal lives is good in congenital heart block. In a series of 8 cases that Campbell<sup>1</sup> followed for nine years he reported 2 deaths. The average sur-

vival rate for the other 6 patients was twenty-two years on last examination. The ages of these patients ranged from twenty-two to forty-two years. Jaleski and Morrison<sup>7</sup> reported a case in a thirty-one-year-old woman with congenital complete heart block who went through two terms of pregnancy and delivery without any complications. Levine<sup>8</sup> mentions a fifty-five-year-old patient who was known to have had complete heart block since the age of six, probably of congenital origin. The optimistic outlook in congenital complete heart block mentioned above should be contrasted with life expectancy in acquired heart block. The studies of Campbell<sup>6</sup> and Graybiel and White<sup>9</sup> show that approximately 70 per cent of patients with acquired heart block died less than three years after the discovery of the lesion. The remaining 30 per cent were alive after an average of six to seven years.

### SUMMARY

Two cases of complete heart block, probably congenital in origin, in veterans of World War II are presented.

The significant clinical aspects of congenital complete heart block are discussed.

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## VACCINATION AGAINST INFLUENZA A AND B\*

## A Comparison of Reactions, Doses and Titer Responses of Two Different Vaccines in Infants and Children

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ALTHOUGH numerous investigators have reported success in protecting adults from influenza A and B, very few studies are available in infants and children. A quantitative evaluation of the titer responses in this age group to various doses and types of vaccines was undertaken, as well as a study of the local and systemic reactions

## METHOD

The inoculations of vaccine were given subcutaneously from 9 to 10 a m. Temperatures were taken at four-hour intervals, and changes were computed by comparison with the patient's previous temperature record. The maximum rise was

TABLE 1 Temperature Elevations

VACCINE	DOSE	MEAN OF MAXIMUM ELEVATIONS F	RANGE OF MAXIMUM ELEVATIONS F	SUBJECTS WITH SLIGHT ELEVATIONS*		SUBJECTS WITH MODERATE ELEVATIONS†		SUBJECTS WITH MARKED ELEVATIONS‡	
				NO.	PER CENTAGE	NO.	PER CENTAGE	NO.	PER CENTAGE
1	0.5	1.19	-0.2 to +4.6	25	53	17	36	5	11
2	0.5	0.48	-0.4 to +1.6	34	79	9	21	0	0
1	1.0	1.12	-0.2 to +4.0	10	43	15	30	5	10
2	1.0	0.59	-0.4 to +4.0	35	76	10	22	1	2

\*Less than 1 F

†1.0 to 2.9 F

‡3.0 F or higher

to the vaccines. Adams, Thigpen and Richard<sup>1</sup> showed that the immune response to influenza A infection was equally great in young infants and older children.

A group of 245 children, ranging in age from one to sixteen years and interned in one building for residua of poliomyelitis, were the subjects of this study. The children were divided into five groups, all of which were nearly comparable in age distribution. The first two groups received 0.5-cc and 1-cc doses of vaccine 1 ¶. The second two groups received the same doses of vaccine 2 ||. The fifth group was not vaccinated, but early and later serum titer studies were done as in the first four groups. This study was carried out in November and December, 1946.

determined in each of 186 cases, as well as the mean maximum for each group.

The local reaction was evaluated immediately, and at intervals of approximately twenty-four hours for thirty days.

Samples of blood were obtained before the vaccine was given and fourteen days after its administration. The viruses used in the quantitative titer determinations were those of influenza A (PR 8 strain) and influenza B (Lee strain). The photoelectric densitometer was employed after the method described by Hirst and Pickels.<sup>2</sup> All the four hundred and fifty-six determinations were done in pairs and in large lots.

## RESULTS

## Temperature

The means of the maximum temperature elevations are presented in Table 1. The values show that 0.5 cc of a vaccine gave the same average temperature rise as 1 cc of the same vaccine. Vaccine 1 caused a significantly higher temperature response than vaccine 2. Many children receiving the former had temperatures well over 100°F. The maximum temperature elevation occurred most frequently eight to twelve hours after vaccination.

## Local Reaction

The injection of vaccine 1 caused a sharp, stinging pain, which lasted a few minutes and then subsided.

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¶This vaccine, which was prepared from egg cultures of influenza A (PR 8 and Weiss strains) and B (Lee strain) viruses by erythrocyte adsorption and elution, was kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

||This vaccine, which was prepared from egg cultures of influenza A (PR 8 and Weiss strains) and B (Lee strain) viruses by calcium phosphate adsorption, was kindly supplied by Parke Davis and Company, Detroit, Michigan.

Vaccine 2 caused little or no immediate pain. The local reaction was measured and palpated at intervals, and although there was considerable variation, the following general observations were made twenty-four hours after the injection of vaccine 1: there was a small area (1 or 2 cm.) of erythema,

TABLE 2 Frequency of Systemic Reactions to Influenza Vaccine

VACCINE	DOSE cc	TOTAL NO OF SUBJECTS	SUBJECTS WITH REACTIONS	
			NO	PERCENTAGE
1	0.5	39	11	28
2	0.5	48	3	6
1	1.0	49	10	20
2	1.0	48	8	17

which was slightly swollen and indurated and moderately tender. At forty-eight hours there was usually minimal or no local reaction remaining. Twenty-four hours after the administration of vaccine 2 there was an area of erythema, which, on the average, was significantly larger (2 to 10 cm.) than that caused by vaccine 1. Also, the local site was usually more swollen and indurated, and in a

quent, reactions were observed with vaccine 1. The least number of systemic reactions occurred with 0.5 cc. of vaccine 2. A convulsion occurred in a one-year-old girl who received 1 cc. of vaccine 1.

No unquestionably positive reaction was observed in any of the 60 children who were given skin tests. Difficulty in interpreting skin tests with the undiluted vaccine was encountered because of the irritative properties of the formalin contained in the material used. (None of these subjects are included in the titer studies.) Curphey<sup>3</sup> has reported a fatal allergic reaction to influenza vaccine. Ratner and Untracht<sup>4</sup> cited several allergic reactions and recommend that all patients be tested with 0.02 cc. of the undiluted vaccine before vaccination. Protamine-precipitated vaccine,<sup>5</sup> like that of calcium phosphate adsorbed, apparently contains less allergenic substance than the vaccine prepared by erythrocyte adsorption. A newer vaccine prepared by centrifugation<sup>6</sup> is said to be virtually free of substances causing allergic reactions.

Antibody Titers

The increase in the antibody titer is indicated by the ratio of the late to the early value rather than

TABLE 3 Frequency Distribution of Titer Ratios

VACCINE	DOSE cc	INFLUENZA VIRUS	SUBJECTS WITH INCREASE OF LATE OVER EARLY TITER				TOTAL NO OF TITER PAIRS	GEOMETRIC MEANS OF INCREASES
			LESS THAN 2 FOLD	2 TO 3 FOLD	4 TO 7 FOLD	8 TO 50 FOLD		
1	0.5	A	14	3*	7	3	27*	2.4 fold
2	0.5	A	14	5	1	2	22	3.5 fold
1	0.5	B	8	8	6	5	27	1.9 fold
2	0.5	B	9	7	2	4	22	2.9 fold
1	1.0	A	11	7	3	1	22	2.1 fold
2	1.0	A	5	3	4	2	14	4.1 fold
1	1.0	B	4	6	6	5	21	3.0 fold
2	1.0	B	1	2	3	7	13	7.8 fold
(Control)		A	30	0	0	0	30	1.0 fold
(Control)		B	30	0	0	0	30	1.0 fold†

\*Of the 27 titer pairs against influenza A in the group receiving 0.5 cc. of vaccine 1, there were 3 with late titers showing an increased range of 2 to 3.9 fold over the early titers.  
†1.0 fold represents no increase in the late over the early titer.

few subjects the whole upper arm was tender. At the end of forty-eight hours a definite subcutaneous nodule had formed in most of the subjects receiving vaccine 2. This was still present thirty days later in a few cases.

Systemic Reactions

The number of systemic reactions is recorded in Table 2. The ages of the children with reactions ranged from thirteen months to nine years in the group given 0.5 cc. of vaccine 1, three to thirteen years in the group given 0.5 cc. of vaccine 2, sixteen months to sixteen years in the group given 1 cc. of vaccine 1 and two to fifteen years in the group given 1 cc. of vaccine 2. The principal reactions were headache, restlessness and wakefulness. In general it was concluded that severer, as well as more fre-

quent, reactions were observed with vaccine 1. The frequency distribution of all the cases in terms of the number of fold increase of the late titer over the early titer (late to early ratio)

In view of the fact that the titers increase in a geometric fashion, the geometric mean was employed in the group comparisons, and the statistical calculations were made on the basis of logarithms. The geometric means for the titer increases are included in Table 3. All the means in the groups receiving vaccine were significantly higher than those in the control group. Except for the mean increase of 7.84 against the virus of influenza B in the group receiving 1 cc. of vaccine 2, in which the number of patients was too small and the range of values too great to justify an accurate comparison, there was no significant difference

between the groups. For example, 1 cc of a vaccine was no better than 0.5 cc of the same vaccine, nor was vaccine 1 better than vaccine 2 from this point of view. There did not appear to be any differences in the titer response of the younger compared to the older children. The titers against the virus of influenza B were generally higher than those against the virus of influenza A.

### DISCUSSION

The subjects in our study were not exposed to an epidemic of influenza, so that the value of the vaccinations was not tested clinically. A fairly consistent rise in antibody titers was demonstrated in the majority of the vaccinated group as opposed to the controls. Henle, Henle and Stokes<sup>7</sup> have shown greater protection against the disease in the persons with the high titers. The majority of the subjects whose titers failed to rise appreciably (less than twofold) had high initial levels.

All the inoculations were given subcutaneously. Van Gelder and his associates<sup>8</sup> concluded that the intracutaneous route produced better titer responses. No subject in our study received more than one injection. The antibody level reached after one dose was as high as that observed after two doses according to a study reported by Hare and his co-workers.<sup>9</sup>

The second blood sample was drawn after fourteen days in all subjects. These titers probably did not represent the maximum level in each case because of varying host responses as well as the differences in vaccines used.

In our experience, the vaccines employed were safe for infants and children in the doses employed, and with one exception, in which a large dose was given to a one-year-old child, no severe reactions were observed in the 245 subjects. The question of the use of influenza vaccine in the practice of medicine remains for the individual physician to answer. Certainly, it may be offered as giving protection of some degree to most persons, since its value has now been attested by several reports, including that of the Army Influenza Commission.<sup>10</sup> The administration of any vaccine entails an occasional unfavorable reaction. Whether or not this militates against its use in practice cannot be decided here, but its value as a public-health measure can hardly be questioned when the morbidity and mortality figures in large cities after influenza epidemics are studied. The uncomplicated disease except for pandemics probably is not responsible for death, but it is one of the common precursors of

pneumonia, which takes its toll after every influenza epidemic. The pandemics of influenza recorded in medical history have been responsible for more deaths than any scourge known to man. One of the probable causes of pandemics is a world-wide susceptibility. It seems possible that extensive use of influenza A and B vaccine will offer man some protection against pandemic as well as epidemic influenza and against the high mortality associated with this disease.

### SUMMARY

A comparative study of reactions, doses and antibody titers has been made with two different vaccines against influenza A and B in infants and children.

The temperature elevations were significantly higher with vaccine 1 than with vaccine 2, although the dose of the vaccines did not appear to make any appreciable difference. Vaccine 2 caused more local reactions, such as swelling and tenderness at the site of inoculation, whereas the systemic reactions appeared to be more intense with vaccine 1.

A definite increase in the antibody titers was demonstrated in the majority of the vaccinated subjects as compared to the controls, but no significant difference between the vaccines was observed.

There was no significant difference between the titers obtained with 0.5 cc and 1 cc of the same vaccine. Children under three years of age, in our opinion, should not be given more than 0.5 cc of vaccine.

The decision whether or not to use influenza vaccine is left to the individual physician.

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ACUTE MENINGITIS CAUSED BY *NEISSERIA SICCA*\*

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THE gram-negative diplococci such as *Neisseria catarrhalis* and *N. sicca*, commonly found in the pharynx, rarely cause meningitis. However, upon occasions they have been proved to be the sole cause of the disease.<sup>1-10</sup> The following case of meningitis due to *N. sicca* was proved by culture and serologic examination §

R. L., a 6½-year-old boy, entered the hospital on January 20, 1947, with a history of sore throat, frontal headache, fever and vomiting of 24 hours' duration. The temperature had risen to 104°F, the headache had increased in severity and he had developed a stiff neck a few hours before admission. The patient had received several doses of sulfadiazine at home, but most of this had been lost in the vomitus.

The past and family histories were noncontributory except for left internal strabismus since infancy.

Physical examination revealed a well developed and well nourished child, who was drowsy but conscious and cooperative. There were no abnormal eye findings except for the left internal strabismus. The fundi were normal. Definite spinal and nuchal rigidity were elicited. The mucous membrane of the throat was somewhat inflamed. The ears were normal. The posterior cervical lymph nodes were slightly enlarged. No petechiae were noted. A bilateral Kernig reflex was present. The blood pressure was 100/70.

Examination of the blood showed a red-cell count of 3,930,000 and a white-cell count of 15,200, with 86 per cent neutrophils, 12 per cent lymphocytes and 2 per cent eosinophils. A blood culture was negative, as was a tuberculin patch test. An x-ray film of the chest was normal. The blood sulfadiazine level ranged from 9 to 15 mg per 100 cc. A lumbar puncture was done and 10 cc of cloudy spinal fluid, under increased pressure, was obtained. The initial pressure was equivalent to 280 mm of water, the dynamics were normal. Examination of the spinal fluid disclosed a white-cell count of 4150, with 84 per cent polymorphonuclear leukocytes, 16 per cent lymphocytes and a total protein of 80 mg, sugar of 83 mg and chloride of 720 mg per 100 cc. A direct smear demonstrated many pus cells but no organisms, a culture showed *N. sicca*.

As soon as the diagnosis of meningitis had been established the patient was given sodium sulfadiazine intravenously and penicillin intramuscularly. Because the previous vomiting had resulted in some dehydration, 5 per cent glucose in physiologic saline solution with 1/6 molar lactate was given intravenously. In the evening of the 2nd hospital day, the urine was noted to be grossly bloody, and sodium sulfadiazine was therefore discontinued. Streptomycin (125,000 units every 3 hours) was started, and 1/6 molar lactate was continued intravenously to keep the urine alkaline — 24 hours later the urine was free of blood.

On the day after admission the patient showed considerable improvement, and he was able to retain food. Penicillin was given intrathecally (5000 units in 5 cc of physiologic saline solution) on the 2nd and 3rd days. The urine contained red cells on the 3rd hospital day but was normal thereafter. On the 4th hospital day, there were no clinical signs of meningitis. Streptomycin was discontinued, and at that time oral glucosulfadiazine was given without any further untoward effect. The patient continued to improve. Penicillin was discontinued on the 9th, and glucosulfadiazine on the 11th hospital day. The spinal fluid on discharge was

clear, with 4 white cells per cubic millimeter, 100 per cent lymphocytes, a sugar of 49 mg per 100 cc and a total protein of 36 mg per 100 cc, culture was negative.

Serum agglutination with *N. sicca* demonstrated a positive titer in a dilution of 1:384 (control, negative) 12 days and one of 1:384 (control 1:96) 61 days after the onset of the acute illness. The titer was negative for both patient and control 154 days after the onset.

## DISCUSSION

The initial diagnosis in this case was meningococcal meningitis, in view of the presence of clinical meningitis with cloudy spinal fluid, which on direct smear showed many pus cells but no organisms. The diagnosis was further strengthened by the report of the presence of a gram-negative diplococcus obtained from the culture of the spinal fluid. However, the laboratory soon reported that the organism isolated did not agglutinate with any of the strains of meningococci available. Subsequently, this organism was identified by the laboratory of the Worcester Public Health Department and confirmed by the laboratory of the Massachusetts Department of Public Health as *N. sicca*.

The possibility of contamination of the spinal fluid was entertained, but on inquiry it was found that this organism is a very rare contaminant.<sup>11</sup>

The question of determining whether the patient had developed immune bodies to this organism was then investigated. Because *N. sicca* tends to clump spontaneously in the presence of physiologic saline solution, the antigen was prepared by a special method to minimize this phenomenon. The organism was grown on nutrient agar slants and incubated at 35°C for forty-eight hours. The slants were washed off with tap water as a precautionary measure to avoid automatic precipitation of the organism. The harvest was collected and ground up with fine sand,<sup>12</sup> and the suspension was allowed to stand for one hour. The supernatant fluid was decanted through cotton, and the suspension diluted with tap water to a No. 8 McFarland nephelometer standard of approximately 2,400,000,000 organisms per cubic centimeter. The antigen was then killed at 60°C for one hour. No preservative was added. The routine slow macroscopic tube agglutination test was used, as described by Kolmer and Boerner.<sup>12</sup> Inasmuch as there was a small but definitely noticeable amount of antigen precipitation in tap water, a positive reaction was assigned only to tubes that showed marked clearing with the formation of large flakes.

It will be noted that twelve and sixty-one days after the onset of acute symptoms, the organism

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§Suggested by Dr. Raymond H. Goodale, pathologist, Worcester City Hospital.

was agglutinated by the patient's serum in a dilution of 1:384. Approximately five months after the illness the titer had dropped to a normal level. The control serums were presumed to be normal and were obtained from men between the ages of twenty and twenty-three years. The finding of a titer of 1:96 in one of the control serums cannot be definitely explained, except by the fact that the control subject may have had a recent infection with *N. sicca*.

On review of the literature it was found that meningitis due to *N. sicca* has been reported only in the course of an endocarditis caused by this organism.<sup>6-7, 10, 12</sup> In the 5 reported cases of endocarditis, symptoms of meningitis occurred in 3, and a positive spinal-fluid culture was found in 1.<sup>7</sup> All these cases of endocarditis terminated fatally except 1 in which recovery followed the use of heparin and sulfapyridine.<sup>6</sup>

Several cases of meningitis caused by *N. catarrhalis* have been reported<sup>1</sup> and also some cases caused by atypical *Neisseria*.<sup>2, 3, 4, 8, 10</sup> The comparative rarity of meningitis caused by this group of organisms suggests a low pathogenicity but modifies the older concept of this group as non-pathogenic.<sup>14</sup>

#### SUMMARY

A case of acute meningitis caused by *Neisseria sicca* is reported. The organism isolated was identified by two different laboratories. An attempt was made to determine the titer of antibodies in the

patient's serum, cultures of the organism being used as the antigen. Although the serologic method available was not entirely satisfactory because of the characteristics of this organism to clump spontaneously, significant titers indicating antibody formation were obtained. Approximately five months after the onset of the acute disease, the titer had dropped to a normal level.

It is believed that this is the first straightforward case of acute meningitis caused by *N. sicca* and uncomplicated by any other infectious process such as endocarditis described in the literature.

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## MEDICAL PROGRESS

### CANCER

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AS a result of public interest, large sums of money have become available in the field of cancer, from state and federal sources and from charitable foundations, and it seems probable that the interest and funds will continue for a long time. The money has been used for stimulation of research, for cancer education among the laity and the medical profession and for direct service to the patient in the form of improved diagnostic and therapeutic facilities.

#### RESEARCH

The literature of laboratory cancer research has become so voluminous that it is virtually impossible for anyone to undertake to digest it all. The Fourth International Cancer Research Congress presented representative contributions in all the principal fields of investigation. Cowdry's<sup>1</sup> recent summary of the Congress ably recapitulates the major fields of interest.

#### EDUCATION

##### *Undergraduate*

Although a considerable part of a medical-school curriculum deals with cancer, and with basic sciences essential to an understanding of cancer, it is true that in many medical schools there has been little or no attempt to correlate the various components in such a way as to give the student a coherent conception of cancer. A committee of the National Advisory Cancer Council has urged the desirability of co-ordinating the teaching of cancer in medical schools, offering financial support for schools presenting acceptable plans of instruction. Several schools have already adopted the recommendations of the committee, and it is anticipated that others will recognize the merits of the proposals.

##### *Graduate*

Fellowships offered by the National Advisory Cancer Council are intended to train men at the resident level to be cancer specialists. The rather rigid requirements of training in surgery, radiology and pathology make it difficult for many hospitals to fit these fellowships into existing resident training programs. In addition, the fellowships come into conflict with the requirements of many of the specialty certification boards. Some relaxation and

elasticity of the program would probably result in better training of more men.

The American College of Surgeons, at the annual clinical congress and in the sectional meetings, offers special sessions and symposia in cancer. These meetings bring to a large audience a condensed review of recent important advances in the cancer field. The series of special articles appearing in the *Journal of the American Medical Association*,<sup>2</sup> with the co-operation of the American Cancer Society, is designed to bring a concise presentation of cancer subjects to the general practitioner. These articles will be assembled in a book, which will assure their preservation.<sup>3</sup> The announcement of a new journal *Cancer*, under the sponsorship of the American Cancer Society, to include a thorough abstract section in addition to original contributions, is welcome news to all who are working in this field.

##### *Public*

Lay education in cancer has been promoted by various groups, notably by the Women's Field Army of the American Cancer Society. There can be no question that as a result of such education, many patients seek medical advice earlier than they would have done otherwise. They are also likely to require a more thorough examination from their physician. Indeed, the demands of the laity have emphasized the necessity for improved cancer teaching for the profession. The public interest stimulated by lay education has in large measure helped to make available the funds referred to above, and to some degree has given the laity a voice in the projects for which the money is used. The public demand has also been responsible for the development of detection clinics.

#### DETECTION CENTERS

It is a basic postulate that the earlier a cancer is detected and treated, the greater is the likelihood of cure. It is also true that the earliest stages of most cancers give rise to no symptoms. Thus, it would be desirable to have some test to which the apparently healthy person could be submitted that would detect cancer in its earliest stages. The only present test that can be employed is a complete and thorough examination. The more thorough the examination, the greater is the likelihood that cancer will be detected in its early stages. Practical considerations of time, personnel and expense impose

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limitations on the thoroughness of the examination. It is apparent that the initial examination must be relatively brief and inexpensive, and that this preliminary screening may be expected to segregate for more extensive study the group most likely to show positive findings.

In regular medical practice the most significant finding on screening is the presence of a symptom or symptoms. Indeed, a patient in general exercises this screening test and consults a physician or goes to a clinic because of a symptom. The physician can then carry out the more thorough investigation necessary to discover the cause of the symptoms. In doing so, he may uncover cancer or some other disease. Without the stimulus of symptoms to be explained, examinations may become perfunctory or routine. Statistics must be available regarding the number of cases of cancer found during the routine physical examinations of applicants for life insurance or of men selected for military service. Statistics are available concerning the expected incidence of cancer in various age groups at a given time.<sup>4</sup>

In response to public pressure, under the sponsorship of various foundations, numerous centers have been established for the detection of cancer. The American College of Surgeons has defined standards for these centers and gives approval to those complying with the standards.<sup>4</sup> Most of the centers report a much higher incidence of cancer than the calculated expected frequency.<sup>4</sup> It is probable that this is due to the inclusion of a large number of persons who are not in fact free from symptoms, and that the centers are serving to this extent as cancer clinics rather than as detection centers.

The centers also reveal a very great number of other conditions requiring medical treatment.<sup>7</sup> These findings may be compared with the number of rejections for physical reasons of men selected for military service. Proponents of the centers consider that many of the nonmalignant conditions encountered are precancerous, and that prompt attention to them prevents the development of cancer. This viewpoint involves a rather broad concept of precancerous conditions.

Although it is premature to evaluate cancer-detection centers, the experiences should be dispassionately reviewed from the standpoint of expense of operation in relation to cases found at a significantly early stage. Follow-up studies of the cases with negative findings should give information regarding the number of cases overlooked. It may well be found that greater numbers of early cancers can be found with less expense of time and money by intensified education of the laity to report early symptoms and of the medical profession to evaluate these early symptoms.

#### DIAGNOSIS

Interest in cytologic methods of diagnosis from smears continues unabated,<sup>8-11</sup> although many

orthodox pathologists preserve a commendable reluctance to accept the findings without reservation.<sup>12</sup> The application of this technic to permit early evaluation of the efficacy of radiation treatment of carcinoma of the cervix, proposed by Graham,<sup>13</sup> may prove to be valuable in the selection of cases requiring surgical intervention. A series of 280 aspiration and punch biopsies was reported by Ellis,<sup>14</sup> with "useful results" in 63 per cent. Meatheringham and Ackerman<sup>15</sup> reported 300 aspiration biopsies on lymph nodes. In 69 aspirations no lymphoid tissue was obtained. A positive diagnosis of carcinoma was made in 147 specimens, and cancer subsequently developed in 32 cases in which the aspiration specimen was negative. Several authors express a warning against aspiration biopsy in possibly operable lung tumors, because of the danger of pleural implantation. Isaacson and Rapoport<sup>16</sup> reported a series of 34 cancer patients who presented an eosinophil count of more than 10 per cent. It is not generally realized that this degree of eosinophilia may be caused by cancer. In 90 per cent of cases multiple metastases were present.

#### LYMPHATIC SPREAD

There has been considerable interest in recent years in amplifying and confirming knowledge of the pathways of lymphatic spread. The brilliant studies of Gilchrist and David<sup>17</sup> on the lymph node metastases of carcinoma of the colon and rectum have greatly influenced the concept of the radical operations for dealing with these cancers. Similar methods of study were employed by Coller, Kay and MacIntyre<sup>18</sup> in cancer of the stomach, colon and rectum. Sweet<sup>19</sup> has contributed to knowledge of the lymphatic spread of carcinoma of the esophagus. Warren and Tompkins<sup>20</sup> have drawn attention to the correlation between prognosis and the numerical extent of lymph-node metastases. Whereas it is generally conceded that lymph-node involvement is usually embolic rather than by permeation, it is evident that the concept of permeation frequently influences the plan of operation, and it remains true that removal of the regional lymphatic vessels en bloc along with the primary focus is an ideal cancer operation when it is feasible.

#### SURGICAL TREATMENT

Critical review of autopsy material discloses that in many cases death from cancer is due to the local extension of the disease, with interference with the functions to adjacent normal organs, rather than to widespread metastatic involvement. Realization of this fact, in conjunction with the general lowering of mortality and morbidity after radical surgery, has led to increasingly radical operative procedures to cope with advanced stages of local disease. Although these operations are too recent to permit evaluation of long-term cures, they offer the possi-

bility of cure in many cases hitherto regarded as inoperable, and in most cases find justification at least as effective palliative procedures. While Brunschwig has written extensively on this subject, the tendency is evident in almost all fields of cancer surgery.

### ORAL CANCER

No single report indicates the trend in the field of oral cancer, but many surgeons are reviving the concept of a one-stage operation for lesions of the tongue, floor of the mouth and cheek, with simultaneous neck dissection and, when necessary, resection of the jaw. These operations can be applied to some cases considered inoperable by conventional standards. Since the procedures are based upon the concept of spread by permeation, which is not the usual method of lymphatic involvement from these cancers, in many cases they show no advantage over the two-stage operations currently practiced. In addition, in coping with inoperable intraoral lesions, they must demonstrate results more satisfactory than those now obtainable by intensive radiation. Although these radical operations undoubtedly have a place, it is likely that their field of employment will be a restricted one.

### CERVICAL-LYMPH-NODE METASTASES

There has been increased willingness on the part of certain surgeons to carry out radical neck dissections bilaterally, with a short interval between the two sides. This procedure involves sacrifice of both internal jugular veins, as well as the anterior and external jugular veins, and is not without danger of causing cerebral damage. In most cases it is probably safer to preserve the internal jugular vein on one side, and it is usually possible to do so. Sugarbaker and Gilford<sup>23</sup> recently drew attention to the combination of neck dissection and jaw resection in cases in which lymph nodes present fixation to the mandible. This procedure has been employed in many clinics, and the dangers of postoperative complications of shock, hemorrhage, sepsis and pneumonia have diminished.

### CARCINOMA OF THE LARYNX

New et al<sup>24</sup> have reported the excellent results obtained by radical surgery in carcinoma of the larynx. Whereas it is true that many of the early cases are amenable to radiation therapy, there is agreement that laryngectomy is the procedure of choice in more advanced cases,<sup>25, 26</sup> and there is evidence that subradical surgical procedures are more effective than radiation in most early cases.

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bility of cure in many cases hitherto regarded as inoperable, and in most cases find justification at least as effective palliative procedures. While Brunschwig has written extensively on this subject, the tendency is evident in almost all fields of cancer surgery.

### ORAL CANCER

No single report indicates the trend in the field of oral cancer, but many surgeons are reviving the concept of a one-stage operation for lesions of the tongue, floor of the mouth and cheek, with simultaneous neck dissection and, when necessary, resection of the jaw. These operations can be applied to some cases considered inoperable by conventional standards. Since the procedures are based upon the concept of spread by permeation, which is not the usual method of lymphatic involvement from these cancers, in many cases they show no advantage over the two-stage operations currently practiced. In addition, in coping with inoperable intraoral lesions, they must demonstrate results more satisfactory than those now obtainable by intensive radiation. Although these radical operations undoubtedly have a place, it is likely that their field of employment will be a restricted one.

### CERVICAL-LYMPH-NODE METASTASES

There has been increased willingness on the part of certain surgeons to carry out radical neck dissections bilaterally, with a short interval between the two sides. This procedure involves sacrifice of both internal jugular veins, as well as the anterior and external jugular veins, and is not without danger of causing cerebral damage. In most cases it is probably safer to preserve the internal jugular vein on one side, and it is usually possible to do so. Sugarbaker and Gilford<sup>23</sup> recently drew attention to the combination of neck dissection and jaw resection in cases in which lymph nodes present fixation to the mandible. This procedure has been employed in many clinics, and the dangers of postoperative complications of shock, hemorrhage, sepsis and pneumonia have diminished.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 34171

#### PRESENTATION OF CASE

A thirty-year-old man, a store clerk, entered the hospital with a complaint of pain in the stomach.

Six months prior to entry the patient noted a dull, heavy, nonradiating, epigastric pain, which occurred in the morning and after meals. It was relieved in part by alkalies and warm milk. There was no nausea or vomiting and no tarry stools, and only a rare stool contained bright-red blood. There had been no anorexia or weight loss. About a week before admission a dull, constant, nonradiating pain in the left flank suddenly developed. Two days prior to admission there was a dull, aching pain in the hypogastrium. This was intermittent in character and resembled the epigastric pain.

Physical examination showed a well developed and well nourished man who was moderately distressed because of hypogastric pain. The lungs were clear to percussion and auscultation. The heart was not enlarged, and no murmurs were heard. There was tenderness in the abdomen to deep pressure, localized mainly just to the left of the umbilicus. Pressure on that area also produced pain in the

back. There was no rebound tenderness. In addition, there was definite costovertebral-angle tenderness on the left and in the region of the left kidney. The liver and spleen were not palpable. There was thought to be a group of matted lymph nodes at the base of the left jugular vein.

Examination of the blood disclosed a hemoglobin of 13 gm and a white-cell count of 8200, with 77 per cent neutrophils. The urine was normal. A stool specimen gave a negative guaiac reaction. The total protein was 7.4 gm, the nonprotein nitrogen 27 mg per 100 cc, the chloride 98 milliequiv per liter, and the serum amylase 16 units.

On the day of admission a gastrointestinal series revealed a 5-cm filling defect on the greater curvature in the prepyloric region. No ulceration was observed, and peristalsis did not pass through the area. A smear and gastric washings showed no malignant cells. An intravenous pyelogram performed on the third hospital day was not entirely satisfactory because of gas and fecal material in the overlying bowel, but demonstrated a delayed secretion of the dye on the left, with a moderate degree of hydronephrosis and hydroureter. Two days later a retrograde pyelogram again showed a left hydronephrosis and some degree of obstruction to drainage of the opaque medium. On the sixth hospital day a gastroscopy showed the greater curvature to be distorted by red, edematous rugae. There appeared to be spasm over this area, and no peristalsis was present. There was a superficial ulceration on the lesser curvature, which measured 1 mm in depth and 1 cm in diameter. The appearance described extended about halfway up the body of the stomach and then ended rather abruptly. On the eighth hospital day the patient vomited reddish-brown material and had severe, colicky pain in the left flank that persisted.

On the twelfth hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR DANIEL S ELLIS It seems to me that it is very clear that this patient had disease involving the stomach and left urinary tract, and I judge that the same disease involved both organs and that it was a malignant process of some kind. I do not know what kind of operation was performed—whether he had a biopsy or whether he was operated on with the idea of attacking the stomach or left urinary tract. Perhaps the x ray films will help in determining the nature of the lesion in the stomach, and also reveal the location of the obstruction in the left urinary tract.

DR STANLEY M WYMAN Examination of the stomach shows the antrum and prepyloric region to be constantly deformed. On the greater curvature there is a constant pressure defect, which elevates the antrum and prepyloric region. The mucosal folds in the lesser and greater curvatures appear unusually thick and prominent. One can see no definite destruction of the mucosa, however. The duodenal loop is not remarkable, but there is deformity of the cap consistent with an old ulcer. The two films from the pyelogram show a slight degree of hydronephrosis on the left with blunting of the minor and major calyces, and widening of the ureter and pelvis. The ureter is traced to the body of the fourth lumbar vertebra. There is no obstruction to that point, and there are no visible stones to account for the dilatation. A single film taken from the retrograde examination shows more clearly the hydronephrosis, which has a generalized character with some delay in the passage of dye at the ureteropelvic junction. No definite obstruction of the ureter can be seen. The kidney outline cannot be adequately detected. The kidney is not displaced in position, and there is no evidence of a pressure defect on the kidney itself. The lung fields and heart are not remarkable.

DR ELLIS Is there any evidence of a soft-tissue mass at the base of the neck?

DR WYMAN No, not in this one film.

DR ELLIS It seems to me that there is no question that if we can ever interpret symptoms as being typical of certain diseases, this patient had a peptic ulcer or ulceration in the stomach, and the original symptom of a dull, nonradiating epigastric pain occurring postprandially early in the morning and relieved by alkalies and warm milk is that of an ulcerating lesion in the stomach. The pain seemed to change very definitely and became hypogastric and related to the region of the left kidney. As far as I am able to determine there are no other clues.

I suppose that a simple peptic ulcer can be fairly well ruled out on the basis that both the gastroscopist and the radiologist who examined the patient thought that there was an extensive lesion involving the lower part of the stomach in the prepyloric

region. Therefore, I believe that this patient had a malignant lesion involving both the stomach and the retroperitoneal lymph nodes and the left ureter, causing hydronephrosis. Such a condition must have been a carcinoma or a lymphoma of some kind. On the law of averages a patient thirty years old ought not to have carcinoma of the stomach, and it is much more likely that he had a lymphoma. The types of lymphomatous disease possibly involving the stomach and the lymph nodes are reticulum-cell sarcoma, lymphosarcoma and, much less likely, Hodgkin's disease. Still another possibility is tuberculosis, of which there seems to be no indication. If this patient's symptoms were first related to the stomach, I think that he had a prepyloric lesion, which was primary in the stomach and metastasized, involving the left urinary tract, causing pressure on the left ureter, with secondary hydronephrosis, and I shall put lymphosarcoma as the first choice. Having had two cases of renal-cell carcinoma before me today, I suppose I am on the spot to say that this is a third case of renal-cell carcinoma, since things usually come in threes. I think that a primary renal tumor with metastases involving the stomach would be less likely than the other way around—that this was a primary carcinoma of the stomach with metastases involving the left urinary tract. I do not believe that this was a scirrhus type of cancer such as one sees in *linitis plastica*, although it was certainly an infiltrating lesion from the description.

I shall conclude by saying that this man had lymphosarcoma, primary in the stomach, with metastases involving the retroperitoneal lymph nodes and causing partial obstruction and increasing obstruction to the left ureter. And if he really had lymph nodes in the neck I shall interpret them as further evidence of that diagnosis. If he had Hodgkin's disease or leukemia, I would expect to have some clue from the blood smears, but there are none recorded for me to base such a diagnosis on.

DR EDWARD B BENEDICT I do not remember this case, but from the description I do not believe it is correct to say that I saw the prepyloric area and described the region of the antrum. As I read the description given, there was an ulcer on the lesser curvature, probably in the body of the stomach.

DR ELLIS It is reported by you and the roentgenologist that no peristalsis was seen in the lower portion of the stomach.

DR BENEDICT It probably means that I did not see the antrum and pylorus.

DR ELLIS From the x ray studies and the way I read this summary I interpret them to signify involvement of the lower end of the stomach by an infiltrating type of lesion.

## CLINICAL DIAGNOSIS

Lymphoma involving the stomach wall and retroperitoneal tissues?

## DR ELLIS'S DIAGNOSES

Infiltrating malignant tumor of stomach, probably lymphosarcoma, with metastases to retroperitoneal nodes

Left hydronephrosis secondary to metastatic involvement of left ureter near left renal pelvis

## ANATOMICAL DIAGNOSES

*Mucous carcinoma of stomach, signet-ring type*

Metastases to mesenteric and retroperitoneal lymph nodes

Obstruction of left ureter from external pressure

Hydronephrosis, left

Congenital hypoplasia of kidney, right

## PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY This patient was explored by Dr Gephart and a large tumor mass found that involved half the stomach, a portion of the omentum and extended down to the region of the left kidney, which appeared to be entirely involved in the same mass. A biopsy of the tumor showed that it certainly was not lymphoma. It was an epithelial tumor with large vacuolated cells, somewhat suggestive of but by no means typical of renal-cell carcinoma, it was so reported.

The patient was transferred to another hospital, where he died a few days later. The post-mortem examination, kindly made available to us by Dr John J Larkin, the pathologist, showed a scirrhous signet-ring carcinoma of the pyloric half of the stomach. A shallow ulceration was present on the anterior wall. The tumor had grown through the gastrocolic omentum to involve the colon and had metastasized extensively in the mesenteric and retroperitoneal lymph nodes. A group of these enlarged nodes surrounded the left ureter, obstructing it by pressure and so producing a hydronephrosis. The right kidney was very small, perhaps congenitally hypoplastic, and also showed hydronephrosis. The right ureter was dilated.

## CASE 34172

## PRESENTATION OF CASE

A forty-seven-year-old woman entered the hospital complaining of pain in the left leg.

She was well until one year prior to admission, when she developed pains in the neck and back, had a gradual loss of energy, easy fatigability and an increased appetite, and had frequent loose bowel movements associated with an urgent gastrocolic reflex. There was slight exaggeration of all these

symptoms in more recent months. Six months before entry she had a barium enema, which was said to have been negative. Two weeks prior to admission the patient had several short chills and ran a slight fever. Five days prior to admission she developed discomfort in the left calf, which persisted until entry. She also had some transient pain in the right leg and during that time ran a temperature of 101°F. Upon entry she was unable to walk because of severe pain in the left calf. She gave no history of hemoptysis, nausea, vomiting or tarry stools.

Physical examination revealed a very obese woman, weighing 230 pounds. There was moderate tenderness in the left leg, extending from the ankle to 8 cm above the knee. The left calf was swollen from 1 to 2.5 cm more than the right calf. There was a positive Homans's sign in the left leg, and there were distended veins over the dorsum of the left foot. The rest of the physical examination was essentially negative.

The temperature was 99.5°F, the pulse 95, and the respirations 18. The blood pressure was 145 systolic, 90 diastolic.

Examination of the blood disclosed a hemoglobin of 13 gm and a white-cell count of 10,700, with 82 per cent neutrophils. The urine was normal. The sedimentation rate was 38 mm in one hour. The prothrombin time was 24 seconds (control, 17 seconds).

The patient was immediately started on a course of anticoagulant therapy, beginning first with heparin and then changing to dicumarol. A chest film was interpreted as negative for previous pulmonary infarcts. The fever continued, the temperature spiking to 101°F in the next few days. On the second hospital day a sharp pain developed in the left lower anterior portion of the chest, with radiation to the shoulder. A friction rub developed over this area in the chest. The prothrombin time after anticoagulant therapy was elevated to 50 seconds. The stools showed a ++++ guaiac reaction. On the seventh hospital day the patient again developed severe pain in the right calf and showed a positive Homans's sign on that side. On the ninth day a bilateral superficial femoral-vein ligation was done under local anesthesia. No thrombi were seen in the vessels. A chest film now showed linear shadows of increased density in the left costophrenic angle and possibly a small amount of fluid. The patient was placed on penicillin because of the development of a cough, with the production of a large amount of mucoid white sputum, and also the presence of rales at both lung bases. Four weeks after admission there was an exacerbation of an acute phlebitis in the left leg. The leg was painful and swollen and was about 10 cm greater in circumference than the right leg at the popliteal space. These symptoms developed under dicumarol, which

was therefore discontinued and heparin instituted. The white-cell count had risen to 23,400, with 88 per cent neutrophils. Another x-ray film of the chest showed that the left costophrenic shadow had become more linear, and there was also a small area of increased density in the posterior portion of the right lower lobe. In the fifth week pain again developed in the anterior portion of the chest, and a slight, but unmistakable, jaundice appeared. The serum albumin was found to be 2.7 gm per 100 cc, and the alkaline phosphatase was normal. The cephalin-flocculation test was +++ Munich bile was present in all the stools, many of which also showed a +++ guaiac reaction. The van den Bergh test was 2.3 to 3.3 mg per 100 cc.

An additional history revealed that one month before entry a sharp pain had developed in the right upper quadrant, associated with anorexia, heart burn and a sensation of epigastric pressure. During that period the patient had lost approximately 14 pounds. In the seventh hospital week epigastric tenderness appeared, and a questionable mass was palpable over the area of maximal tenderness in the left portion of the epigastrium. Bile continued to be present in the urine and the stools. The total protein was 4.2 gm per 100 cc, and the van den Bergh was 15.5 to 21.2 mg per 100 cc. The mass in the epigastrium was thought to have enlarged, but because of the marked obesity of the patient it could not be well outlined. Throughout the latter part of the patient's course the legs had become markedly swollen and edematous. She weighed 270 pounds terminally, and the edema had extended well up into the back. On the sixtieth hospital day the patient became restless and hyperexcitable, the respirations slowed, and she died.

#### DIFFERENTIAL DIAGNOSIS

DR. REEN A. HARWOOD: May we see the x-ray films?

DR. STANLEY M. WYMAN: This is the film taken on admission. It shows no definite evidence of intrinsic pulmonary disease. The right leaf of the diaphragm is higher than the left—higher than one would expect. The heart shadow is not unusual for a patient of this type. The second set of films, taken ten days later, shows the right leaf of the diaphragm even higher. The films were taken in the supine position, however. There is some indefinite density in the left costophrenic angle, and I believe that there is some fluid in the left pleural cavity. In the lateral film there is a suggestion that the right cavity also has a small amount of fluid in the posterior costophrenic sinus. Eight days later the film still shows indefinite linear density in the left costophrenic angle. It has become smaller, however, and there is some linear density in the right middle lung field. It seems to lie in the base of the right upper lobe anteriorly, close to the chest wall. There is a suggestion of an indefinite

round shadow posteriorly in one of the costophrenic sinuses—I believe the right. The next examination still shows density in the anterior base of the right upper lobe and the round density in the base probably of the right lower lobe. There is still fluid in the left pleural cavity and possibly in the right. The final film taken one month after this examination shows the right leaf of the diaphragm to have been elevated, considerably more so than on the previous examination. It is the only available film taken at that time. It makes one wonder about something going on beneath the diaphragm.

DR. HARWOOD: Would you say that the x-ray films are consistent with small pulmonary infarcts?

DR. WYMAN: They are consistent with multiple infarcts at the base of the right upper lobe and possibly of the left lower lobe.

DR. HARWOOD: The mention of jaundice is the first intimation that there was anything else present in this patient besides thrombophlebitis and multiple small pulmonary infarcts.

I do not get a very clear picture of what the illness was like after the appearance of jaundice. Obviously, she must have been very sick. Was that last film taken with a portable machine?

DR. WYMAN: Yes, it is a film taken at the bedside about seven weeks after the initial films.

DR. HARWOOD: The patient was probably too sick to have intensive studies such as a gastrointestinal series. There must be something in the record that would give additional information. Perhaps in summarizing the history some of the negative data were not included.

DR. MYLES P. BAKER: The alkaline phosphatase was elevated quite significantly at the first determination when she was mildly jaundiced, the figure was 14 or 17 units per 100 cc. The cephalin-flocculation test was not +++ on the first observation, it was either + or ++, and I believe that the thymol-turbidity tests were negative at first. Perhaps that is of some importance. It is true that the patient was too sick for further x-ray studies. During the period of increasing jaundice she was entirely aware of what was going on and doing her best to meet the doctors' requests, taking carbohydrates and so forth, and never presented the picture of a person in severe liver failure.

DR. HARWOOD: Was she conscious to the last day?

DR. BAKER: Yes.

DR. HARWOOD: This is one of those interesting cases in which the patient comes in for one complaint, and then, under observation, much more serious disease develops from which the patient dies. I tried, for a short while, to connect the complications with the initial complaints and wondered if she could possibly have had thrombophlebitis of the vena cava. I know very little about this condition, but I think that, if she had had a thrombosis of the vena cava that propagated beyond the entrance of the renal veins, she would not have survived such

an insult for more than a few days, so I ruled that out. Then there was the possibility of a thrombosis of the portal vein. The standard textbooks have very little to say about this, but they speak of the classic symptoms of hematemesis, ascites and severe upper abdominal pain — not a word about jaundice. I suppose that it could cause jaundice, but the information we have does not suggest portal thrombosis. For one thing, we do not know whether she had ascites. Perhaps Dr. Baker can give a little help on that. I think the weight gain of 40 pounds is rather sensational in a person who had such a serious disease, and I suspect that she had ascites as well as massive edema.

DR. BAKER: The patient had such marked edema over the back, loin and flank that it seemed as if she must have ascites, but the percussion note was resonant well over into the side of the abdomen, and one would have to say that the physical signs were not those of ascites, although it was suspected and some observers thought that it was present.

DR. HARWOOD: I am going to guess that she had ascites, but usually in portal thrombosis, the ascites develops rapidly, the taps very often are bloody, and the acute disturbance ordinarily leads quickly to death.

We have to admit that this patient had something wrong with the liver. The evidence of that is the low serum protein found in the fifth week of hospitalization, the positive cephalin-flocculation test and the rising serum bilirubin in the absence of obvious biliary obstruction. The question is, What was the matter with the liver? Did she have cirrhosis of the liver? That is one possibility, with polygonal-cell failure as a cause of the increasing jaundice and death. Dr. Baker has said that she did not present the picture of liver failure. One would expect a different type of death, perhaps a much deeper jaundice, and unconsciousness for several days before death. It seems to me that this diagnosis has been excluded.

Could the patient have had a partial obstruction of the common bile duct, as by stone, or a tumor in the region of the ampulla or in the head of the pancreas? Again, I think not, because at no time did she have clay-colored stools. She could not have developed this degree of obstructive jaundice without clay-colored stools. Obstruction of the common duct from any cause thus seems ruled out.

What are the other possibilities? I suppose that metastatic disease is fairly likely. To go back over

the record, "she developed pain in the neck and back, had a gradual loss of energy, easy fatigability and an increased appetite, and had frequent loose bowel movements associated with an urgent gastrocolic reflex," which suggest to me the possibility of some lesion of the upper gastrointestinal tract, or possibly a lesion in the pancreas.

The onset of carcinoma of the pancreas is apt to be insidious. The history does not quite fit that picture. Pancreatic carcinoma can metastasize to the liver, and I suppose it is possible for a situation to develop in which the metastases are largely in the left lobe, pressing on some of the larger bile ducts of the left lobe, whereas those of the right lobe, being uninvolved, permit the passage of bile.

One thinks of carcinoma of the stomach. Again, it does not fit the picture of the complaints that this woman had for a year before admission. The only thing that might fit is the one symptom of the presence of blood in the stool. She had it nearly every time the stool was examined. A carcinoma of the stomach or possibly somewhere else in the gastrointestinal tract might be the explanation of blood in the stools, and metastases to the liver might be the explanation of the jaundice. I have ruled out carcinoma of the large bowel because of the negative barium enema.

I should mention one final possibility, or rather, still another possibility, because there can be no "final" possibility in a case like this — that is, carcinoma of the gall bladder, the common duct or the ampulla. In all these cases jaundice is an early symptom, and it is usually complete. I think these diagnoses have been excluded because there was bile in the stools.

I have not mentioned primary carcinoma of the liver. This condition is most often found as a complication of cirrhosis of the liver. There is some evidence that this patient had cirrhosis, and it is possible that a primary tumor of the liver was also present. Such a diagnosis does not explain the blood in the stools, but this finding could be explained either by the elevated prothrombin time or by portal hypertension.

Although I am far from sure what this woman had, I am going to make diagnoses of cirrhosis of the liver, with a primary carcinoma of the liver, mostly involving the left lobe, thrombophlebitis of the veins of the lower extremities, possibly of the iliac veins, and multiple pulmonary emboli. I am

going to add a second choice — a carcinoma of the pancreas with metastases to the liver

**A PHYSICIAN** What is the possibility of liver abscess? The diaphragm was elevated. Perhaps there was some fluid there.

**DR HARWOOD** I meant to ask about the chart, but I am sure that Dr Baker would have told me if she had had a high temperature.

**DR BAKER** During the period of active phlebitis, the first week, she had a persistent fever, which subsided later.

**DR MAURICE FREMONT-SMITH** I want to say a few words about this patient, because I was in charge of her health for ten years up to the time of the last illness, including the beginning of it. Looking back, I realize that something happened that we always try to prevent. I cannot see any way now that it could have been prevented. She was a very high-strung woman, who had a tendency to diarrhea. When I first saw her, ten years ago, she had alternating periods of diarrhea and constipation. This continued off and on during the ten years that I took care of her. The diarrhea was affected by the environment. It stopped entirely after any problem that was puzzling her cleared up. Two years before admission to this hospital I did a rectal examination, and a little material being on the end of the glove, I smeared it on a slide, as I always do, and did a guaiac test, which was ++++. Two more specimens of stool were examined, and one was faintly positive and the next negative. On the basis of this blood I insisted that she have a proctoscopy and a barium enema. The proctoscopy was done by Dr Donaldson, who was able to go the full distance of the proctoscope. The mucosa was normal. No injection, ulceration or tumors were seen, except some small hemorrhoids, which were thought sufficiently bulbous and engorged to account for the bleeding. That was approximately a year before entry. Four months later the patient again had a positive guaiac test, and I wrote to her at that time "The chances, of course, are very great that there is nothing wrong except the hemorrhoids. On the other hand, we dare not make this assumption. You should have a barium enema and proctoscopy and so forth." At that time the hemoglobin was normal. Barium enema, a month later, was, as stated in the record, absolutely normal, the colon filling rapidly without constant defects or diverticula.

**DR BAKER** The picture of this woman's last illness, as far as the jaundice is concerned, was that

she was gradually developing extrahepatic obstruction, judging from the laboratory tests. She had had phlebitis in both legs, and we could not really study her adequately. There was a gradual increase in the evidence of liver-cell damage. We wondered at first about the possibility of common-duct stone, recognizing the impossibility of surgery in the presence of the illness unless faced with absolute necessity. The appearance of tenderness in the epigastrium was important. The epigastric mass became more and more obvious, and was not only tender but also the site of persistent pain. Shortly before she died it became obvious that the liver was huge.

**DR HARWOOD** In view of the information that Dr Fremont-Smith has added, may I change my diagnosis?

**DR TRACY B. MALLORY** Certainly.

**DR HARWOOD** I shall put carcinoma of the upper gastrointestinal tract — let us say of the stomach with metastases to the liver — as my first choice, and keep carcinoma of the pancreas as my second choice. Hepatoma now seems very unlikely.

**DR EDWARD HAMLIN, JR.** The only thing that Dr Harwood has not dwelt on is the rather extraordinary lack of efficacy of the treatment for phlebitis. The patient had adequate therapy by both anticoagulins and despite that developed more phlebitis. The veins were tied off at a time when neither vein showed thrombosis above the level of ligation. One would ordinarily assume that the phlebitis at least would not jump the gap. Despite adequate therapy with dicumarol, the lesion went on and both iliac veins became thrombosed. That is unusual and of some importance.

**DR HARWOOD** Suggesting a metastatic nodule pressing on the vena cava?

**DR HAMLIN** Suggesting some deficiency somewhere.

#### CLINICAL DIAGNOSES

Carcinoma of liver, metastatic, primary source undetermined, probably pancreas  
Iliofemoral phlebothrombosis  
Pulmonary infarcts

#### DR HARWOOD'S DIAGNOSES

Carcinoma of stomach  
Metastatic carcinoma of liver  
Thrombophlebitis  
Multiple pulmonary infarctions

## ANATOMICAL DIAGNOSES

*Adenocarcinoma of ascending colon, with metastases to liver*

*Thrombophlebitis of both femoral and iliac veins and of inferior vena cava*

Pulmonary emboli, multiple, with pulmonary infarction

Dependent edema

Ascites, slight

## PATHOLOGICAL DISCUSSION

DR MALLORY Post-mortem examination showed an enormous liver, weighing over 5 kg, completely replaced by metastatic carcinoma. Only very tiny patches of normal liver tissue could be found anywhere within the organ. The primary site of the tumor was in the ascending colon 3 cm above the ileocecal valve — a region where x-ray examination with a barium enema is ordinarily very accurate.

Both common iliac veins, as Dr Harwood predicted, were thrombosed, and thrombus also extended up the vena cava, practically to the mouths of the renal veins. The lower portion of the thrombus in the vena cava showed a considerable degree of organization, indicating that it had been present for a considerable time. There was massive edema of both legs and of the sacral and back regions, undoubtedly primarily dependent on thrombosis of the vena cava. The patient was perfectly vulnerable to vena-cava obstruction because she had had a previous hysterectomy, with consequent destruction of both ovarian veins, which are two of the most important sources of collateral circulation for obstruction of the inferior vena cava. She had had multiple pulmonary emboli, and these had produced

a series of infarcts in the lung, some of which were old and completely scarred, and others in all stages of more recent development down to one quite fresh one that must have occurred only a few days before death.

DR FREMONT-SMITH Was there any ascites?

DR MALLORY There was only 800 cc of fluid, which would not have been detectable in this particular patient on physical examination. Whether the extreme enlargement of the liver was sufficient to produce functional obstruction of the vena cava and thereby increase the tendency to thrombosis I cannot answer with certainty.

DR F DENNETTE ADAMS The tumor itself might account for it.

DR MALLORY There were no actual tumor nodules that could be seen pressing on or obstructing the vena cava.

DR ADAMS I meant that the presence of cancer anywhere in the body more or less tends to facilitate thrombosis.

DR FREMONT-SMITH How large was the tumor in the cecum?

DR MALLORY A small annular lesion at the time of autopsy.

DR HAMLIN To go back to the phlebitis. Despite the fact that the prothrombin time without therapy was elevated and despite the further elevation produced by anticoagulants she went on to thrombosis. I am not aware of any comment in the literature that the presence of an overwhelming malignant lesion will produce phlebitis, but it is certainly the impression of people like Dr Allen that such lesions cause phlebitis. The very fact that this rather paradoxical situation took place indicates that an overwhelming malignant tumor was present.

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## BRITISH MEDICINE AT THE CROSSROADS

THE National Health Service Bill of Great Britain was enacted by Parliament on November 6, 1946, and unless changed by Parliament will become effective on July 5, 1948. It will take British medicine a long mile down the left-hand road—in company with the rest of Britain's institutions.

According to this act the Minister of Health is made responsible for setting up a service that is intended to improve the "physical and mental health of the people of England and Wales, and the prevention, diagnosis, and treatment of illness, and for that purpose to provide or secure the effective provision of services. These services will be rendered free of direct cost to the recipients.

The Ministry of Health is also charged with indirect responsibility for organizing and maintain-

ing General Medical Services, Health Centers, and all other health services, such as Maternal and Infant Welfare, Home Nursing and Midwifery. All doctors may join the new services, none are required to. Remuneration is settled by regulation and is made up of a "fixed part-salary" and a capitation fee, the latter decreasing as the number of a doctor's patients rises. The sale of practices, long an accepted transaction in Great Britain, is prohibited.

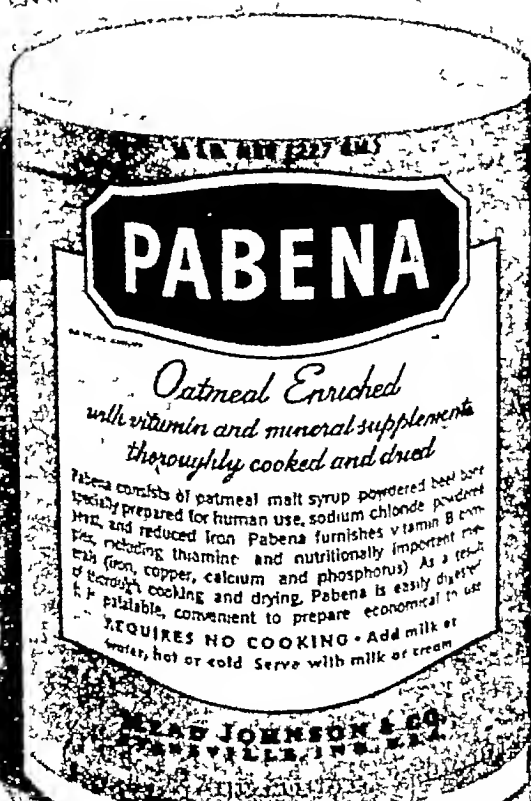
The opponents of the act point out that it means centralization of authority in the office of the Minister of Health (and England has had five Ministers of Health in seven years), intervention of a social worker between doctor and patient, the promise to its beneficiaries of complete medical, dental and nursing services without obvious cost, and the creation of a great lay bureaucracy to administer the program. It means also an estimated cost of at least \$1,800,000,000 during 1948 and, inferentially, the ultimate enslavement of all physicians, dentists and nurses into salaried government positions.

A year ago the British Medical Association, as conservative as cold roast beef was once considered to be, held a plebiscite on the act and voted 23,110 against it and 18,972 in favor, with 14,589 members abstaining. On January 31, 1948, a second plebiscite was held that resulted in a vote of 40,814 against the act, or 89.5 per cent of those voting, and 4,735 in favor of it. Another year of socialism, combined with an unfortunately dictatorial attitude on the part of Aneurin Bevan, the present minister of health, has served to crystallize the opinion of British doctors.

It is difficult to know how much of this stiffened resistance is due to an awakened appreciation on the part of the British Medical Association of what the profession stands to lose when the act goes into effect, and how much it may be the result of Mr. Bevan's apparently unco-operative and dictatorial attitude. From the debates that have taken place on the act one is forced to the conclusion that Mr. Bevan's methods have been coercive and his attitude impolitic even to the point where his judgment seems at times to be under the domination of his emotions. Win, lose or draw in this contest, it would seem that the medical profession of Great



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## AN EVALUATION OF CURARE IN SPASTICITY DUE TO SPINAL-CORD INJURIES\*

ROBERT A. KUHN, M.D.,† AND DONALD S. BICKERS, M.D.‡

FRAMINGHAM, MASSACHUSETTS

IN 1850 Claude Bernard<sup>1</sup> demonstrated the site of action of curare to be the neuromuscular junction. His experiments have been verified by numerous investigators, and in 1935 West and King<sup>2</sup> clarified the mode of action and enumerated the pharmacologic properties of the drug. It was not until 1943 that Wintersteiner and Dutcher<sup>3</sup> crystallized the quaternary ammonium salt, d-tubocurarine chloride. Recent availability of this pure preparation has stimulated clinical and pharmacologic investigations.

The gross effects of curare on the normal human subject have been thoroughly investigated. The intrinsic musculature of the toes and eyes demonstrates early paresis, which successively involves the muscles of the limbs, head and neck. Inter-costal muscle relaxation is soon followed by paralysis of the diaphragm. During the early stages of curarization, the patient complains of blurring and fuzziness of vision. The eyelids droop, diplopia develops, and the jaws relax. There is weakness and heaviness of the neck muscles progressing to head drop. Further administration of the drug produces complete peripheral paralysis and, finally, respiratory arrest.<sup>4</sup> These signs and symptoms disappear in reverse order, and the rate of disappearance is dependent upon the nature of the curare preparation administered.

Although it is known that curare exerts its influence primarily at the myoneural junction, the exact mode of action remains in doubt. Eccles, Katz, and Kuffler<sup>5-10</sup> demonstrated that the end-plate potential in fully curarized muscle rises to sub-threshold levels and subsides without initiating muscle response. The size of the potential—that is, the degree of depolarization—depends in part on the concentration of the curare in the muscle. The degree of block is controllable, and certain frequencies can be suppressed. This action may well explain obliteration of various involuntary move-

ments while normal voluntary contractions continue.<sup>11</sup>

Clinically, curare has been used with value in a number of conditions necessitating muscle relaxation. Curare therapy of tetanus has met with some success,<sup>12-15</sup> and convulsions incident to shock therapy are effectively diminished.<sup>16-18</sup> However, it is in anesthesiology that this drug has achieved its maximal usefulness to date. In 1942, Griffith<sup>19</sup> reported the use of curare as an adjuvant to general anesthesia, and numerous excellent studies in succeeding years have thoroughly established its value in this field.<sup>20-23</sup>

In 1942 Denhoff and Bradley<sup>24</sup> conducted a controlled study of the effectiveness of aqueous curare in relieving the spasms of children with cerebral palsy. They concluded that progress under physical therapy was definitely accelerated in these subjects. Muscular relaxation with maximal therapeutic dosages was maintained for a period of approximately four days. Burman,<sup>25</sup> Bennett<sup>26</sup> and Schlesinger<sup>27</sup> reported similar success in patients exhibiting spasticity and rigidity.

Recent reports have indicated that curare might offer valuable aid in the amelioration of spastic paraplegia and paraparesis.<sup>21, 28, 29</sup> Schlesinger<sup>27</sup> administered aqueous curare to 11 patients with extreme spasticity due to spinal-cord injuries and obtained excellent but transient relaxation. A suspension of d-tubocurarine chloride in a peanut-oil and white-wax mixture was prepared in an effort to retard the rate of absorption. The curare effect was found to be prolonged up to three days in some cases, and effective reduction of spasticity was not accompanied in any case by unpleasant side reactions. The effect of the curare in oil on patients exhibiting voluntary function masked by spasm seemed more dramatic than that observed in paraplegic patients.

Severe spasm of muscle groups innervated below the level of the cord lesion is frequently a major manifestation of spinal-cord injury, whether due

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The views expressed in this article are those of the authors and do not necessarily represent those of the Veterans Administration.

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Here, and elsewhere in this article, the term "spasticity" refers to the involuntary muscular contractions occurring in strict *à muscle groups* innervated below the level of the cord lesion. More detailed descriptions of these myoclonic events are given in the case reports presented below.

extension in the lumbar spine for normal hip motion while splinted by his spastic muscles. This is not efficient ambulation and is never recommended as the procedure of choice, but only as a last resort under these circumstances.

The height of the back brace has been the subject of much discussion and experiment, but the optimum level has proved to be 4 cm below the inferior angle of the scapulas. This is sufficiently high to allow good articulation with the lower portion of the thoracic cage and yet low enough to permit free action of the scapulas and other elements of the pectoral girdle. Higher back braces are superfluous since the thoracic cage is well supported structurally by ligaments and the pectoral girdle. A positive objection to braces extending above this point is the

ward. Unless a caliper lock is employed in addition to stabilize this ankle joint, some stability may be sacrificed. This is justifiable since it means the difference between a brace that is practicable for use and one that is not.

### Miscellaneous (Fig 7)

In patients whose injuries occur above the first thoracic segment, certain special appliances may be made for the arms, depending upon the degree of brachial-plexus involvement. Among these are the triceps brace to maintain the arms in extension and a leather wristlet to maintain wrist stability. The knee strap is used when necessary to prevent genu varus or valgus, and the "T" strap performs a similar function at the ankle joint. The cock-up splint is made of a wire frame with transverse canvas web supports.<sup>7</sup> The sleeper brace and cock-up splints are used in the earlier stages (I and II) before the patient becomes ambulatory as an aid in preventing flexion contractures of the ankle and knee. The detachable spreader bar is occasionally employed in teaching the swing through in Stage IV, but further use is discouraged; it is attached to the medial uprights at ankle level by means of bolts with wing nuts. The Taylor back brace, not shown, is used for correction in the occasional case in which severe kyphosis develops in high thoracic and cervical injuries.

### DISCUSSION

It will be noted in the foregoing discussion of the four general types of supports that the indications are based primarily on the assumption of a complete lesion at the level indicated. Although such an injury is actually present in the majority of patients, a smaller proportion of incomplete injuries of the cord and cauda equina will be encountered. In such cases it is impossible to state categorically in advance exactly what type of appliance will be indicated, not only because of wide variance in the initial pattern of muscular dysfunction but also because there may be gradual improvement in muscular power over a period of months after the initial trauma. Muscle analysis is indispensable in partial lesions as the initial step when the patient is ready for bracing. With this information at hand and the specific function performed by each type of appliance borne in mind, a rational approach may be made to the specific problem presented. In cervical-cord injuries the extent of the brachial-plexus involvement will determine the appliances necessary for the upper extremities.

Although a detailed study of ambulation is beyond the scope of this communication, it is essential in any discussion of braces at least to mention the type of gait that may reasonably be employed with a given appliance. Patients requiring only drop-foot braces approach most nearly the normal gait. They may use ultimately either one or two canes and walk

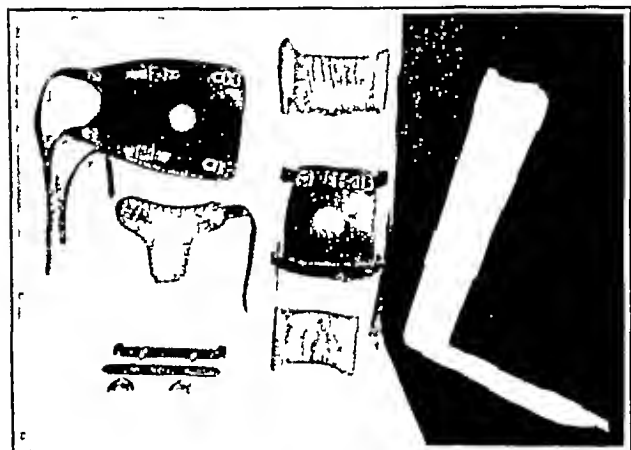


FIGURE 7 Miscellaneous Braces

Upper left, knee strap, middle left, "T" strap, lower left, detachable spreader bar, center, sleeper brace, and right, cock-up splint

interference offered to the proper use of crutches, which become entangled with the back-brace extension. The height has a direct bearing on the total weight, which at best exceeds that of any other type. Attempts to substitute duraluminum for the uprights and transverse struts of the back brace have resulted in failure because of the great stress that the appliance is called on to bear. Some weight may be spared with substitution of sheet duraluminum for the 17-gauge steel in the main body of the back support, but further use of this material is foredoomed to failure.

It was primarily for patients with back braces that the caliper with a detachable drop-foot spring was developed, since the stirrup-type leg brace with shoes and back brace attached requires the assistance of one or two persons in application and removal of the unwieldy device. With calipers and a detachable drop-foot spring the patient can wear shoes continually, insert the calipers into the shoes and then proceed to lace the brace from below up-

almost normally except that they tend to proceed on a rather wide base with steppage gait. Initially, it may be necessary to train such patients with crutches instead of canes, but the use of crutches should be discouraged as rapidly as possible — the obvious objections to crutches are that they call attention to the patient's handicap and promote a feeling of dependency. The type of gait to be employed by patients with long leg braces will depend on the degree of function remaining in the thigh flexors. Should the thigh flexors be adequate to advance the legs even though not strong enough to support the patient's body weight, either the four-point or the more rapid two-point crutch gait is feasible. In either case, he should also be taught the swing through, which is the most rapid of all gaits and may be required in situations in which speed is desirable, as in crossing streets with traffic lights. This type of gait can be taught to any properly prepared patient with a complete or partial lesion below the first thoracic segment and is mandatory for those with loss of thigh flexors and higher lesions (the second lumbar segment upward). The pelvic-band group will not usually exhibit enough function to allow the two-point and four-point gaits and consequently must be taught the swing through with the preliminary temporary swing-to gait. For patients requiring back braces the only practicable gait for distance walking is the swing through, which is taught to all patients except those with lesions above the second thoracic segment that are so severe as to cause gross impairment of arm function. As in the pelvic band group, the swing to is taught as a preliminary to learning the swing through. The swing to is retained only for maneuvering in close quarters where the lack of space renders the swing through impossible. Since the hip joint must be movable for efficient ambulation, it is incumbent on these patients to exercise more skill and balance than lower injuries demand. The patient should not be permitted to attempt a swing to until he has thoroughly mastered the art of balancing with first one and then the other crutch off the floor, unsupported by either an instructor or other artificial means. The poise and sense of confidence gained thereby is basic in the subsequent steps of ambulation progressing through the swing to to an efficient swing through. Lesions high enough to involve the brachial plexus usually force the patient to walk with a swing to or shuffle. This has proved practicable with one of our patients with a complete motor lesion below the fifth cervical segment except for some intact fibers in the seventh and eighth cervical segments. Concurrently and later, all patients must go through a period of intensive mat work and other calisthenics designed to strengthen the pectoral girdle and arms to a point that will permit the stress of weight bearing demanded for ambulation. This is particularly important in the group with higher injuries.

The knee lock used in construction of the long leg braces is recommended after testing of several more complicated types. It is of simple, rugged construction requiring a minimum of machining and repair. The gravity lock is easily placed and fool-proof during use. More elaborate locks are more expensive and prone to damage by twisting or bending.

The width of calf and thigh bands is of practical importance. As a general rule, best results are obtained from narrow bands. Although no difficulties have been encountered, owing to the youth of the patients, circulatory embarrassment may well result in older patients if calf and thigh bands are too wide. This precaution should apply to any patient with venous varicosities, arteriosclerotic changes or other impairment of peripheral circulation.

Steel is the material of choice though its weight is somewhat greater than that of duraluminum. Its durability and capacity to withstand torsion and stress, particularly of the higher braces and in heavy patients, make it irreplaceable by any of the light alloys available. Observations on duraluminum braces constructed here and at other institutions indicate that joints deteriorate rapidly and that twisting necessitates frequent attempts at adjustment, which are rarely, if ever, successful. The calf and thigh bands used on these braces are not of the contour-fitting type advocated by Hessing,<sup>1</sup> since no weight-bearing function is required of them. The considerable time and expense associated with the building of such bands may be avoided.

### SUMMARY

Preliminary rehabilitation procedures prior to the fitting of braces on patients with spinal-cord injuries are outlined.

Factors involved in choosing the proper brace for patients with spinal-cord injuries, with special reference to the level of injury, are discussed.

Four main types of brace are presented in detail, with the indications for each.

The type of gait to be expected for each level is described.

I am indebted to Mr. Walter Gavin of the Orthopedic Shop, Cushing Veterans Administration Hospital, for his co-operation and assistance.

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# ULCEROGLANDULAR TULAREMIA TREATED WITH STREPTOMYCIN

## A Report of Two Cases

CAPTAIN RAYMOND E LESSER, M C, A U S., AND MAJOR SIDNEY MILLER, M C, A U S

HEILMAN'S<sup>1</sup> demonstration of the effectiveness of streptomycin against *Pasteurella tularensis* in vitro and in vivo has found application in the treatment of tularemia in man. The cases presented below are considered to be of interest because they report additional experience with the use of streptomycin in the treatment of tularemia. Furthermore, they afford an interesting comparison of the effectiveness of treatment of the acute and chronic phases of the disease.

### CASE REPORTS

**CASE 1** A 39-year-old man was hospitalized on February 14, 1947, complaining of "cold sensations," pain in the eyes and back and coughing and sneezing of 2 days' duration.

The past history as obtained at the time of admission was of no related significance except for typhoid fever 29 years previously and malaria in 1930.

Physical examination revealed a haggard but well nourished man who appeared moderately ill. The skin was livid

scratched his right middle finger with a briar, but he had not skinned the rabbits. On the following day a localized area of infection was noted at the site. On the day of admission he experienced chills, fever, headache, general malaise and a tender swelling in the right axilla. He also volunteered the information that "rabbit fever, typhus fever and hemorrhagic fever" were endemic in his home town, Americus, Georgia, the locale of his rabbit hunting. Agglutinations and a culture and smear of the ulcerated area were made, and streptomycin — in a dosage of 3 gm daily — was given. Treatment was continued for 7 days. Within 24 hours the patient experienced dramatic subjective improvement, and in 48 hours the temperature began to regress and the lesion to undergo involution. At the end of 7 days the temperature became normal and remained so for the duration of the hospital stay of 54 days. The local lesion and axillary adenopathy completely subsided 4 weeks after the institution of streptomycin.

The subsequent clinical course was uneventful. The pertinent laboratory data are summarized below, and the clinical course is graphically represented in Figure 1.

On February 14 examination of the blood disclosed a white-cell count of 12,000, with 70 per cent neutrophils, 23 per cent lymphocytes and 7 per cent monocytes. The urine was normal. The blood Kahn test was negative. On February 25 a blood culture was negative, and smear and culture of the ulcer were negative for *Past. tularensis*, agglutinations for the organisms of typhoid, paratyphoid and undulant fever, as well as those for salmonella and typhus (proteus x 19), were negative. Agglutinations for *Past. tularensis* were + + + + in a dilution of 1:40, + + + in one of 1:80 and negative in one of 1:160. On March 6 the agglutination was + + + + in a dilution of 1:1280, + + in one of 1:2560 and negative in one of 1:5120. On March 10 the agglutination was + + + + in a dilution of 1:160 and + + in one of 1:1280. On March 19 the agglutination was + + + + in a dilution of 1:320, + + in one of 1:640 and negative in one of 1:1280, and on April 7 it was + + + + in a dilution of 1:160, + + in one of 1:640 and negative in one of 1:1280.

Three x-ray examinations of the chest during the initial 10-day period were negative.

**CASE 2** A 26-year-old paratrooper was hospitalized on April 24, 1946. He complained of right axillary and right epitrochlear swelling associated with numbness of the fourth and fifth fingers of the right hand of 2 months' duration. During that time he had lost 17 pounds in weight and had observed that the "swellings" had been increasing in size, at the time of admission they had become painful. The patient had been rabbit hunting in January, previous to and at the time of which he had had a "sore" on the ring finger of the right hand. After he dressed the rabbits the "sore" on the right ring finger became deeply infected, and red streaks extended to the wrist. Two weeks later he experienced chills and fever. After these symptoms had persisted for 1 week, he reported to another Army installation, where he was treated for malaria, the fever persisting for 1 week after hospitalization. On the day of admission he had noted the onset of aching in the muscles and joints.

Physical examination revealed a well developed man, who showed signs of recent weight loss. There were numerous small, nontender shotty lymph nodes in the anterior cervical triangle. In the right axilla there were three tender nodes, which were rubbery in consistency and measured 1 or 2 cm in diameter. A similar tender right epitrochlear node was present. When palpated, a linear structure that was considered to be the ulnar nerve moved on manipulation of the node and produced a shocking type of ulnar paresthesia. An ulnar hypesthesia of the fourth and fifth fingers was also present. A circular scar, measuring 5 mm in diameter, was on the medial dorsal surface of the terminal phalanx of the fourth finger of the right hand.

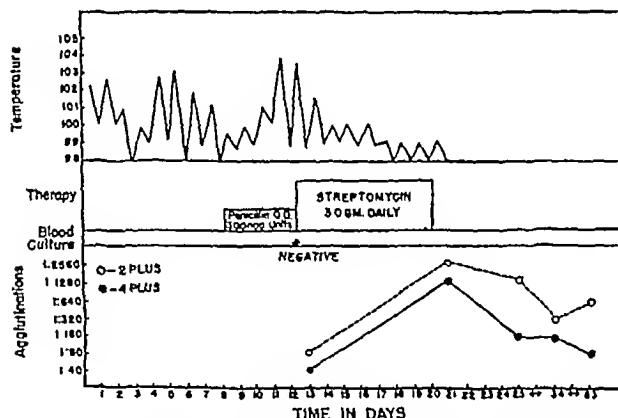


FIGURE 1 Pertinent Laboratory Data and Clinical Course in Case 1

Except for a moderately injected throat and increased breath sounds at the left base, the findings were not remarkable.

On the following day the patient began to manifest a spiking, remittent type of fever. The examining ward officer believed that the patient had a virus pneumonia. When the temperature continued and coarse rales were noted at the left base, previous supportive and symptomatic measures were supplemented by 300,000 units of calcium penicillin in beeswax and peanut oil each day. Despite this therapy the clinical course remained unchanged. Two weeks after admission the examining ward officer first noted an umbilicated, ulcerative lesion with a necrotic center on the dorsal surface of the right middle finger at the distal phalangeal joint, measuring 1.5 cm in diameter. The edges were raised, erythematous and indurated. A single tender, firm lymph node measuring approximately 3 cm in its greatest diameter was palpable in the right axilla. The presumptive diagnosis of tularemia was entertained, and corroborative studies were made.

Further questioning revealed that the patient had been rabbit hunting 3 days before admission. He stated he had

Examination of the blood disclosed a white-cell count of 7500, with 55 per cent neutrophils. A smear was negative for malaria. The urine and the serologic findings were normal. The corrected sedimentation rate was 11 mm in 1 hour (Winthrope method). Two agglutinations for *Past tularensis* were negative. The presumptive diagnosis of tularemia was so strongly held that it was requested that the specimen be sent to the Service Command Laboratory, where agglutinations for *Past tularensis* were reported + + + + in a dilution of 1:320 and + + in one of 1:2560. A ray examination of the chest was negative.

During the hospital stay the patient was afebrile. With the establishment of the diagnosis of tularemia streptomycin therapy consisting of 0.2 gm. every 4 hours for a total of 4.4 gm. over a 4-day period was instituted. During treatment

There was generalized lymph node enlargement, a 1-cm., nontender right axillary node several pea sized tender left axillary nodes, two pea sized nontender right epitrochlear nodes three similar nontender left epitrochlear nodes and bilateral tender inguinal nodes on the left.

The temperature was 97.6°F. the pulse 80 and the blood pressure 110/85.

The patient remained afebrile throughout the hospital stay. Shortly after admission, the left epitrochlear and left inguinal lymph nodes were surgically removed. The former was extracted and cultured on cystine blood agar. However no growth was obtained. The inguinal node was sent to the area pathology laboratory, which reported chronic lymphadenitis. A ray examination of the left hip was negative.

Because of the rise in agglutination titer, as well as the significant change in clinical course it was believed that the

TABLE 1 Agglutination Determinations in Case 2

DATE	1:40 dilution	1:80 dilution	1:160 dilution	1:320 dilution	1:640 dilution	1:1280 dilution	1:2560 dilution	1:5120 dilution
4/25/46	Negative							
4/30/46	Negative							
5/6/46	++++	++++	++++	++++	++	++	++	Negative
5/8/46	++++	++++	++++	++++	++	++	++	Negative
5/14/46	++++	++++	++++	++++	++	++	++	Negative
6/1/46	++++	++++	++++	++++	++	++	++	Negative
6/19/46	++++	++++	++++	++++	++	++	++	Negative
6/26/46	++++	++++	++++	++++	++	++	++	Negative
7/2/46	++++	++++	++++	++++	++	++	++	Negative
7/9/46	++++	++++	++++	++++	++	++	++	Negative
10/12/46	++++	++++	++++	++++	++	++	++	Negative
1/7/47	++++	++++	++++	++++	++	++	++	Negative
2/14/47	++++	++++	++++	++++	++	++	++	Negative
3/1/47	++++	++++	++++	++++	++	++	++	Negative
3/1/47	++++	++++	++++	++++	++	++	++	Negative
3/11/47	++++	++++	++++	++++	++	++	++	Negative
3/14/47	++++	++++	++++	++++	++	++	++	Negative
3/19/47	++++	++++	++++	++++	++	++	++	Negative
4/12/47	++++	++++	++++	++++	++	++	++	Negative
5/7/47	++++	++++	++++	++++	++	++	++	Negative
6/15/47	++++	++++	++++	++++	++	++	++	Negative

\*Streptomycin, in total dosage of 4.4 gm. given between May 11 and 15

†Streptomycin, in total dosage of 12.0 gm., given between March 4 and 11

there was beginning regression of the lymphadenopathy and diminution in the weakness. One week later all tenderness of the lymph nodes had subsided but slight residual adenopathy remained. The patient, who was much improved subjectively, was discharged to duty 35 days after admission.

After discharge he was seen periodically as an outpatient. Objective and subjective improvement continued with complete resolution of the adenopathy and with ability to carry on with military performance. However, he still complained of some weakness and did not completely regain the weight that he had lost.

Determinations of agglutination for *Past tularensis* were made monthly and remained constantly + + + + in a dilution of 1:160 during the ensuing months.

Except for weakness and nausea following exertion the patient remained well until December. He experienced a mild aching sensation in the left thigh, left leg and left lower quadrant. When he arose each morning associated malaise returned. The symptoms were of gradual onset but increasing severity. On January 6 1947 he noted for the first time a recurrence of lymphadenopathy in the left epitrochlear region. At the next dispensary an agglutination for *Past tularensis* was reported as + + + + in a dilution of 1:1280—a higher titer than at any time previously or subsequently in the illness. On February 3 the aching pain in the left axilla and left leg became severe. The leg pain apparently originated in the left inguinal region and was associated with left inguinal adenopathy, the pains radiated down the leg were aggravated by exercise and were relatively constant. A novocain injection into the left groin produced relief for 1 hour. Neuropsychiatric examination revealed no psychoneurotic tendencies.

On February 24 the patient was readmitted to the hospital because of the symptoms and clinical course described above. Physical examination revealed a slightly toxic and chronically but not seriously ill patient.

patient was experiencing a relapse. Therefore on March 4 streptomycin was started, consisting of 3 gm. daily for 7 days in divided doses for a total of 21 gm. At the conclusion of therapy the patient felt markedly improved, and the adenopathy slowly regressed. Previously, he had lost 15 pounds in weight. One month after the conclusion of therapy he had regained 7 pounds. There was no adenopathy and the agglutination determination was + + + + in a dilution of 1:160 and + + in one of 1:320. However the last determinations were + + + + and + + in dilutions of 1:160 and 1:640 respectively, on May 25. Urinalyses were negative during the period of observation. An electrocardiogram was normal. A bromsulphalein test (5 mg. dose) showed no retention of the dye in 1 hour. The corrected sedimentation rate was 9 mm in 1 hour (Winthrope method) on two occasions.

The agglutination determinations are presented in Table 1

## DISCUSSION

The effectiveness of streptomycin treatment in the cases reported above parallels that which has appeared in the literature to date.<sup>1-12</sup>

Case 1 afforded no particular problem once the diagnosis had been established. The response was excellent, so far as both morbidity and mortality were concerned, and the effectiveness of streptomycin was again demonstrated. Case 2, however, presented a more complex problem.

Several features present themselves for discussion. The effectiveness of streptomycin when latency exists between initial onset of the disease and the institution of treatment does not seem to be en-

hanced Although the clinical response to streptomycin was definite, the subsequent course of the disease indicates probable inadequacy of dosage initially It may also indicate decreased effectiveness of treatment when a delay occurs between the initial phase of the disease and the institution of therapy The recurrence of symptoms associated with variation in serologic titer of significant degree suggests that criteria for chronicity should be extended farther than the number of days of temperature above 98.6°F, the duration of buboes and the number of days in bed, as suggested by Foshay and Pasternak.<sup>6</sup> Evidence for relapse as manifested by serologic and clinical changes may be correlated with the retention of living bacteria within the recovered patient The inability of streptomycin to effect lasting remission in Case 2 was probably due not only to this fact but also to development of resistance by the organism to the antibiotic agent The initial amount of streptomycin used may be considered inadequate in the light of current knowledge of organism sensitivity It is unfortunate that such studies were not available in this case, in which the course of events suggests the importance of early control of the disease before maximum invasion has occurred

## SUMMARY

Two cases of ulceroglandular tularemia treated with streptomycin are presented in which the course paralleled that which has appeared in the literature to date

The mechanics for failure to effect a lasting cure in one case are discussed

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## THE EFFECT OF SURGICAL OPERATIONS ON THE BROMSULFALEIN-RETENTION TEST\*

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THERE are several reports in the literature dealing with the effect of surgical operations on liver function. The available material was recently reviewed.<sup>1,2</sup> Most workers report changes in a high proportion of patients after surgery under general or spinal anesthesia. The hippuric acid test was used in several cases but has been criticized on theoretical grounds. The principal objection is that it depends on the integrity of kidney function, which may be impaired immediately after a surgical operation. Other authors have reported results obtained with the bromsulfalein-retention test using an injection of 2 mg. of the dye per kilogram of body weight.<sup>2</sup> It has recently been shown that the bromsulfalein-retention test is rendered more sensitive by the use of a dose of 5 mg. per kilogram of body weight.<sup>3</sup> Finally, in view of the report that mechanical trauma to the liver may produce impairment of its function,<sup>4</sup> it seemed worth while to evaluate the effect on the liver of extra-abdominal operation so as to exclude the possible factor of mechanical trauma.

The work reported below represents an attempt to detect changes in the function of the liver following extra-abdominal operations by means of the bromsulfalein-retention test modified so as to make it more sensitive.

In addition to this procedure blood was obtained for thymol-turbidity and cephalin-flocculation tests.

Bromsulfalein retention was determined on non-fasting patients according to the method of Mateer et al.,<sup>3</sup> 5 mg. per kilogram of body weight and a thirty-minute period being used. Readings of bromsulfalein retention were made by comparator block matching.

The cephalin-flocculation test was done by the method of Hanger,<sup>5</sup> using the Difco reagent. A single twenty-four-hour reading of the reaction was recorded.

In the thymol-turbidity test the technic described by MacLagan<sup>6</sup> was used and the values expressed in cubic centimeters of a suspension of barium sulfate as recommended by Ley et al.<sup>7</sup> The reaction of the thymol reagent as measured by the Beckman electrometer was pH 7.8.

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\$Kindly supplied by Hynson, Westcott and Dunning, Philadelphia. With 5 mg. of dye per kilogram of body weight, a correction factor is used in the readings.

## MATERIAL AND METHOD

A group of 20 patients admitted to the Memorial Hospital for operative treatment was studied. Half the patients (Group I) were on the Head and Neck Service, and the other half (Group II) on the Breast Service. This type of patient was selected to avoid the inclusion of cases in which intra-abdominal procedures had been performed. The possibility of mechanical trauma to the liver was therefore excluded. In each group of 10, the patients were unselected and were studied as they were admitted on the wards.

The state of nutrition of each patient was appraised by means of the history and general appearance, the weight and the detection of clinical signs of nutritional deficiencies. All patients studied were found to be in a satisfactory state of nutrition except 1 (Case 7), who was obese. Clinical evaluation of pre-existing liver damage was done by questioning about the existence of past liver disease, exposure to toxic factors including alcoholism and the detection by physical examination of such signs as enlargement of the liver and spleen, icterus, collateral circulation and spider angiomas. By these criteria, all patients were found to be free of clinically detectable liver disease before and after the operation period except 1 (Case 2), whose liver was slightly enlarged and who had a past history of heavy alcoholic intake.

Two patients, Cases 12 and 14, were found to have high blood pressure on admission. The former had a blood pressure of 170 systolic, 120 diastolic, auricular fibrillation and slight dyspnea on exertion, but no peripheral edema. Functionally she belonged to Group II-C of the classification of the New York Heart Association, her cardiac status was not clinically altered by the operative procedure. The other patient had a blood pressure of 210 systolic, 90 diastolic. Her only cardiac symptom was slight dyspnea on exertion. This case should be considered in Group I-B of the classification of the New York Heart Association; the operation did not alter her cardiac status.

The over-all clinical picture, including the type of operation and its duration, is presented in Table 1. Some patients (Cases 1 to 10) received intravenous pentothal sodium as a general anesthetic, in others (Cases 11 to 20) operation was performed under general anesthesia by nitrous oxide, oxygen and ether. Every patient prior to operation received an injection of 15 mg. of morphine, 0.6 mg. of atropin and 100 mg. of nembutal or 100 mg. of luminal.

In each group the patients were classified according to decreasing severity of operation. Thus in Group I, the most serious operation was performed in Case 1, and the least serious in Case 10. In Group II the most serious operation was performed in Case 11, and the least serious in Case 20. Evaluation of the gravity of the surgical procedure is

admittedly arbitrary and was based mainly on two criteria: extent of trauma, with particular emphasis on bone resection, and duration of the procedure. This classification does not pretend to be an absolute one but rather reflects the general trend of severity within each group.

The blood pressure was followed by readings obtained at fifteen-minute intervals during the entire procedure and immediately thereafter. A fall of blood pressure of 20 to 40 for not longer than half an hour was considered a sign of mild shock. A more serious manifestation of shock was not observed. Replacement fluids given in the course of the operation are indicated in Table 1. Fever was absent at the time of operation in all patients.

On admission the bromsulfalein-retention test was carried out, and blood was obtained for the thymol-turbidity and cephalin-flocculation tests. This procedure was repeated within an hour of the patient's return from the operating room. In most cases the patient was still under the influence of the anesthetic when the second test was done. At least a one-day interval separated the preoperative and postoperative tests. The patient was tested again once or twice several days later when he was well on the way to recovery.

## RESULTS

### *Bromsulfalein Clearance*

Before the operation the retention of bromsulfalein in all patients did not exceed 10 per cent, with the exception of 1 patient (Case 7), who had a retention of 12 per cent. The upper limit of normal retention of bromsulfalein after thirty minutes with the technic used is 10 per cent, and all patients studied can therefore be considered as having had a normal test preoperatively.

Immediately after the operation, there was a marked elevation of the amount of bromsulfalein retained in the blood in several patients; the increased retention could be considered significant in Cases 1 to 9, 11, 12, 14, 15 and 16. The elevation was absent or insignificant in the others. The increased retention was pronounced in 6 cases in Group I (Cases 1, 2, 3, 5, 7 and 8), the greatest retention being observed in Case 8, and in 2 patients in Group II (Cases 11 and 12). The increased retention was not maintained, and the test returned toward normal in the following days.

### *Thymol Turbidity*

The usually accepted upper limit of normal with this test is a turbidity corresponding to 1.75 cc. of barium sulfate suspension. Four of the 20 patients initially had a somewhat elevated test (Cases 1, 11, 14 and 20). There was no general increase after the operation. One patient (Case 7) showed a



significant increase. In the others the thymol turbidity either remained unchanged or decreased.

### *Cephalin Flocculation*

A normal test is represented by absence of flocculation (0) or a + reaction. Five patients (Cases 1, 4, 5, 8 and 10) had an abnormal flocculation test preoperatively. The change in cephalin flocculation postoperatively was not consistent, increasing in some patients and decreasing in others. Most patients in Group II, with the exception of Case 19,

In Group I there was no absolute correlation between the severity of the operation and the amount of dye retained postoperatively. For instance, the patient (Case 8) whose operation was considered less severe than that on the 7 patients preceding her in the classification of Table 1 had the highest degree of retention. In Group II the correlation was better, since the greatest retention of dye was observed in the first patients of the group (Cases 11 and 12). If the two groups of patients are considered together, there seemed to

TABLE 1 *Clinical Data*

CASE No	AGE	SEX	DIAGNOSIS	OPERATION	DURATION OF OPERATION	FALL IN BLOOD PRESSURE	FLUIDS	OTHER DISEASE
	yr				hr		cc	
1	64	M	Squamous cell carcinoma of gingiva	Local excision of tumor and mandible and radical neck dissection	3	0	500 (glucose) 500 (blood)	—
2	57	M	Squamous-cell carcinoma of tongue	Glossectomy-radical neck dissection	4	0	500 (glucose) 500 (blood)	—
3	38	M	Metastatic squamous-cell carcinoma of neck	Radical neck dissection	3½	Mild	3000 (glucose) 1000 (blood)	—
4	54	F	Carcinoma of salivary gland	Resection of maxilla and antrum	1½	0	0	—
5	34	F	Adenocarcinoma of parotid gland	Removal of parotid gland	2½	0	1000 (glucose) 500 (blood)	—
6	54	M	Adenocarcinoma of parotid gland	Removal of parotid gland	¾	0	0	—
7	54	F	Hashimoto struma	Hemithyroidectomy	1	0	500 (glucose)	—
8	60	F	Thyroglossal cyst	Excision of cyst	1	0	0	Epilepsy
9	72	F	Squamous cell carcinoma of tongue	Partial glossectomy	¾	0	0	—
10	49	M	Previous squamous-cell carcinoma of gingiva, surgical defect	Plastic upper lip, skin graft	1	0	0	—
11	44	F	Carcinoma of breast	Radical mastectomy	2¾	0	500 (glucose)	Anemia (hemoglobin of 60%)
12	58	F	Carcinoma of breast	Radical mastectomy	2¾	Mild	500 (glucose)	Hypertensive heart disease, with failure
13	56	F	Carcinoma of breast	Radical mastectomy	2	Mild	500 (glucose)	—
14	60	F	Intraductal papilloma of breast	Local excision	¾	0	0	Hypertensive heart disease, with failure
15	38	F	Periductal mastitis	Local excision	¾	0	0	—
16	32	F	Fibroadenoma of breast	Local excision	¾	0	0	—
17	32	F	Unilateral mastitis	Local excision	¾	0	0	—
18	48	F	Duct papilloma of breast	Local excision	¾	0	0	—
19	47	F	Fibroadenoma of breast	Local excision	¾	0	0	—
20	30	F	Sclerosing adenosis of breast	Local excision	¾	0	0	—

had a normal cephalin flocculation initially, which remained normal postoperatively.

### DISCUSSION

The data show that in 14 of the 20 patients there was a significant increase in the retention of bromsulfalein postoperatively as compared to the amount retained before the operation. The retention of dye was very pronounced in several cases. Whereas all patients, with the possible exception of 1 (Case 7), initially had a normal clearance, the increased retention following the operation in 14 cases resulted in postoperative values that were considered abnormal and indicative of liver dysfunction.

be a correlation between severity of operation and retention of dye, since the last patients of Group II, who probably underwent the least severe type of surgical procedure, also showed the smallest degree of retention postoperatively.

It is obvious that the criteria by which the severity of the operations was evaluated are not absolute, and other factors than the ones considered above may have played a role.

The mechanism by which a surgical operation produces such marked changes in bromsulfalein retention is not entirely clear. Liver dysfunction is a conspicuous and early sign of shock.<sup>8</sup> The early stages of shock may not be manifested by a fall of blood pressure at a time when anoxemia of internal

organs such as the liver and the kidney has already taken place.<sup>8</sup> It is therefore conceivable that although the patients in this series either did not experience a fall in blood pressure or at most showed a slight and transitory fall, they had a certain degree of anoxemia of the liver during the operation, explaining the reduced ability of this organ to clear the blood of dye. In that case, the increased retention of bromsulfalein following an operation might be significant as a measure of the amount of injury inflicted on internal organs by a surgical procedure.

If the changes in bromsulfalein retention observed denoted liver dysfunction, the abnormality appeared to be reversible and did not persist longer than a few days. Normal or nearly normal values were observed in almost all patients a few days after the operation.

So far as the thymol turbidity and cephalin flocculation were concerned, it was not expected that the tests would show any significant change. These procedures depend entirely on the presence of an abnormal globulin constituent in blood plasma, and

TABLE 1 (Continued)

CASE No	BROMSULFALEIN RETENTION					THYMOL TURBIDITY					CEPHALIN FLOCCULATION				
	PRE OPERATIVE	IMMEDIATELY POST OPERATIVE	POST OPERATIVE*	POST OPERATIVE*		PRE OPERATIVE	IMMEDIATELY POST OPERATIVE	POST OPERATIVE	POST OPERATIVE		PRE OPERATIVE	IMMEDIATELY POST OPERATIVE	POST OPERATIVE	POST OPERATIVE	
1	%	%	%	%											
1	—	40	18 (5)	—	2.0	1.5	0.5	—	++++	+++	++	—			
2	4	36	8 (5)	—	1.05	1.25	1.0	—	+	+++	+	—			
3	4	40	6 (4)	—	0.7	0.6	0.5	—	0	++	0	—			
4	10	22	14 (10)	—	0.5	0.5	0.7	—	++	0	+	—			
5	6	32	8 (4)	—	1.7	1.5	1.1	—	++++	++	0	—			
6	6	16	18 (1)	12 (3)	0.8	1.0	1.0	0.8	0	+++	++++	+++			
7	12	32	32 (1)	14 (4)	1.3	2.1	2.0	1.1	0	+++	+	—			
8	0	64	32 (3)	—	0.9	1.2	1.10	—	+++	+	0	—			
9	6	14	4 (14)	—	0.7	0.6	0.5	—	0	++	0	—			
10	4	6	2 (4)	—	1.1	1.0	1.1	—	++++	+++	++	—			
11	10	24	—	—	2.4	0.8	—	—	0	0	—	—			
12	6	40	16 (3)	—	1.0	1.3	1.4	—	0	0	0	—			
13	4	4	4 (4)	—	0.9	0.9	0.8	—	0	0	++	—			
14	6	12	8 (6)	—	2.2	1.2	1.3	—	0	0	0	—			
15	8	16	8 (7)	—	0.7	0.6	0.3	—	0	0	0	—			
16	6	16	6 (7)	—	1.3	1.0	0.3	—	0	0	0	—			
17	4	6	6 (9)	—	1.1	1.3	1.3	—	0	0	0	—			
18	8	10	6 (8)	—	0.2	0.4	0.6	—	0	0	0	—			
19	4	4	6 (8)	—	1.6	1.6	1.3	—	+	++	+++	—			
20	4	6	4 (6)	—	2.1	1.5	1.6	—	0	0	0	—			

\*Numbers in parentheses refer to days after operation.

applied to a distant anatomic region. A direct mechanical trauma to the liver during the operation, as in the course of an intra-abdominal operation, seems to be ruled out in the patients of this series by the type of subjects selected.

The anesthesia may have been a contributory factor, although pentothal and ether are not considered to be liver poisons. Nevertheless, this factor cannot be entirely ruled out. The extent of the surgical procedure and its duration, regardless of the type of anesthesia, appeared to be more important. The data do not indicate that the age of the patients was a decisive factor in the production of postoperative liver dysfunction as shown by the retention of bromsulfalein in the blood.

this could hardly be expected to occur during the relatively short duration of the operation. The absence of definite changes in the two tests during the postoperative period indicates that the liver dysfunction detected by the bromsulfalein test in the series of patients studied was not pronounced, and confirms its transitory nature.

These results largely confirm those obtained by previous workers and indicate definite impairment of liver function after protracted surgical operations, even when the operative site is such that mechanical trauma to the liver is ruled out.

The changes in liver function are probably significant in that they may represent one of the factors contributing to a complex syndrome called "post-

operative disease." The prevention and control of these changes deserve further study

### SUMMARY

There was a significant increase in the retention of bromsulfalein immediately after an extra-abdominal operation in 14 of 20 patients studied. No similar changes were observed in the thymol-turbidity and cephalin-flocculation tests.

There was a certain degree of correlation between the severity of the operation and the postoperative appearance of an impaired ability of the liver to clear the blood of bromsulfalein. Other factors, such as anesthesia by ether or pentothal sodium and the age of the patients, appeared less important. The significance of these facts in relation to the physiologic changes brought about by a surgical operation is discussed.

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## THE PROBLEM OF SULFONAMIDE-RESISTANT HEMOLYTIC STREPTOCOCCI\*

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### BOSTON

PREVIOUS reports have discussed the problem and circumstances of the development of sulfadiazine-resistant hemolytic streptococci in the armed forces of the United States during 1944.<sup>1-8</sup> In a civilian community the occurrence of infections due to sulfonamide-resistant hemolytic streptococci<sup>9</sup> indicates that these organisms have had a wide distribution throughout the general population via military personnel. The possibility that these resistant organisms might become an epidemiologic and therapeutic problem in civilian life cannot be dismissed on the basis of the available information. Also, the likelihood of such a situation arising in the general population — that is, the development of sulfonamide-resistant or penicillin-resistant strains of hemolytic streptococci under the common therapeutic and prophylactic regimens — should be considered, and efforts directed toward its prevention.

A study of the sulfonamide sensitivity of hemolytic streptococci in the general population would indicate the prevalence of known sulfonamide-resistant strains and also whether there are naturally resistant strains that might assume increased resistance under proper circumstances. It is the purpose of this paper to present the results of sulfonamide-

sensitivity determinations of hemolytic streptococci as they occurred in a New England population, as well as an analysis of the available information pertaining to the conditions under which sulfonamide-resistant hemolytic streptococci developed.

### METHODS

The cultures studied were obtained from patients admitted to the Evans Memorial and Haynes Memorial Hospitals, serving Boston and the suburban areas surrounding it, during the fall and winter of 1946-1947. These patients were admitted to the hospital because they had clinical evidence of a streptococcal infection or were admitted for observation or study and found to harbor hemolytic streptococci. Most of the strains of hemolytic streptococci were isolated from the nasopharynx of patients who had clinical scarlet fever, others were obtained from streptococcal carriers or patients with pharyngitis, otitis media, pneumonia or wound infections due to the hemolytic streptococcus.

Cultures were obtained by swabbing of the nasopharynx or infected areas with culture swabs. The swabs were wiped on 2 per cent blood-agar plates, streaked and incubated aerobically at 37°C for twenty-four hours. Single colonies of beta-hemolytic streptococci were picked and transferred to blood-agar plates or to broth for further identification and study. The hemolytic streptococci isolated were grouped and typed by the precipitin technique, antiserums for Types 1 to 47 were available. The

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sulfonamide sensitivity was determined by the method of Wilson,<sup>11</sup> horse serum being used, susceptible and resistant strains were always run as controls. Only organisms growing in a concentration of 5 mg per 100 cc of sodium sulfadiazine were considered to be resistant. Occasionally scant growth appeared in the tube containing a concentration of 1 mg per 100 cc, however, owing to the conditions of this test, growth in this tube was not considered evidence of resistance.<sup>11, 12</sup>

### RESULTS

One hundred and sixty-seven Group A hemolytic streptococcus strains isolated during the fall and winter of 1946-1947 were tested for sensitivity to the action of sulfadiazine. The type distribution and sulfonamide sensitivity are indicated in Table 1. Types 18, 30 and 31 were the most prevalent, however, there was no predominant epidemic-type strain prevalent in this area. Types 1, 17 and 19, which were the predominant types in the Navy,<sup>1, 2</sup> did not assume any epidemic prominence in this study.

Of 167 strains of Group A hemolytic streptococci tested for sensitivity to the action of sulfadiazine, 166 were sensitive to its action—that is, none grew in a concentration of sodium sulfadiazine as great as 5 mg per 100 cc. One strain, a Group A, Type 19 hemolytic streptococcus, was resistant to the action of sodium sulfadiazine in a concentration of 25 mg per 100 cc. This sulfonamide-resistant strain was isolated from a patient who had clinical scarlet fever and later developed electrocardiographic and clinical evidence of rheumatic heart disease. This strain was sensitive to 0.0078 units of penicillin, as determined by the method of Rammelkamp.<sup>13</sup>

### DISCUSSION

Recent publications have offered some suggestions regarding the possible origin of sulfonamide-resistant streptococci.<sup>1, 4, 9, 12, 14, 15</sup> From theoretical points of view these resistant bacteria could exist as naturally occurring variants, they could arise as variants of normally susceptible strains as a result of contact with and adaptation to the drug, or they could arise as spontaneous genetic mutants. Whatever the explanation of this phenomenon, once sulfonamide-resistant variants appear they increase in prevalence in a sulfonamide-containing environment as a result of their greater fitness to survive. It is of interest to determine what light recent clinical and epidemiologic experience has shed on this problem.

Although methods to detect the development of sulfonamide resistance by other bacteria in vitro were known, attempts to demonstrate the resistance of hemolytic streptococci to sulfonamides, by the use of ordinary mediums containing sulfonamide inhibitors, were uniformly unsuccessful.<sup>3</sup> The need for a method of demonstrating sulfonamide re-

sistance in vitro became urgent with the failure of the mass chemoprophylaxis program in the armed forces in 1944. During that year Wilson<sup>11</sup> developed a technic that enabled one to determine the ability of hemolytic streptococci to grow in a semisolid medium free of sulfonamide inhibitor and containing respectively 0, 1, 5, 25 and 125 mg per 100 cc of sodium sulfadiazine. This test conclusively demonstrated the presence of sulfonamide-resistant strains of hemolytic streptococci, which were the cause of increasing numbers of upper respiratory infections while sulfonamide prophylaxis was being carried out in the armed forces.<sup>2, 4</sup>

After the first demonstration of sulfonamide-resistant Types 3, 17 and 19 Group A hemolytic streptococci during a program of mass chemopro-

TABLE 1 Type Distribution and Sulfadiazine Resistance of Group A Hemolytic Streptococci

SEROLOGIC TYPE	NO. OF STRAINS	NO. OF SULFADIAZINE RESISTANT STRAINS
3	1	0
5	1	0
12	3	0
17	4	0
18	6	0
19	3	1*
22	1	0
24	1	0
26	4	0
28	5	0
30	6	0
31	1	0
36	1	0
38	1	0
39	3	0
42	1	0
43	1	0
47	1	0
†	117	0

\*This strain was resistant to the action of sodium sulfadiazine in a concentration of 25 mg per 100 cc.

†Strains not classified by the precipitin method with available diagnostic serum.

phylaxis in the armed forces,<sup>2, 4</sup> it became essential to know if there were any resistant strains before this program was inaugurated in the Navy in December, 1943.<sup>1, 2</sup> This information could be obtained only by tests of cultures that had been preserved prior to this program of mass chemoprophylaxis. No sulfonamide resistance was demonstrated in over 100 of the strains of hemolytic streptococci preserved at the Rockefeller Institute Hospital prior to 1937.<sup>16</sup> Siegel<sup>17</sup> showed that 90 strains of Group A hemolytic streptococci isolated from scarlet-fever patients before 1938 were sensitive to the action of sulfadiazine. Sensitivity determinations on strains of hemolytic streptococci isolated from patients with scarlet fever<sup>12</sup> in the United States Navy prior to December, 1943, did not show any evidence of resistance. Most of these strains were Type 19, and some were isolated from patients who had been receiving small doses of sulfadiazine during a scarlet-fever epidemic in New York City.<sup>18</sup> It should be noted that strains of Type 19 later

appearing in the armed forces were resistant to sulfonamides. From this information it seems safe to conclude that before the program of mass sulfadiazine prophylaxis had been initiated in the armed forces in 1943 there were no known sulfonamide-resistant Group A hemolytic streptococci.

Rantz et al,<sup>14</sup> however, reported the results of testing strains of Group A hemolytic streptococci isolated in the Army from December, 1943, to April, 1944, and observed that some of the typed strains were more resistant than others — that is, that they grew in suspensions of 1 mg and 5 mg of sodium sulfadiazine per 100 cc. The authors were of the opinion that these strains were naturally resistant to moderate amounts of sulfadiazine and were the precursors of the more highly resistant strains such as Types 3 and 17, which later became established as epidemic, resistant strains. The possibility of transfer of these resistant strains to Army personnel by members of the Navy on chemoprophylaxis cannot be ruled out.

Several studies of streptococcal carriers treated with sulfadiazine to rid them of the carrier state are enlightening in demonstrating the possibility of the development of resistance under those conditions of treatment. Strains of hemolytic streptococci isolated from 40 patients before and after treatment with therapeutic doses of sulfadiazine did not show any evidence of the development of resistance to sulfadiazine.<sup>12</sup> Another study of 10 carriers treated with 1 gm of sulfadiazine daily for a ten-week period did not reveal any increase in sulfadiazine resistance of the post-treatment cultures as compared with the pretreatment strains.<sup>17</sup> Hamburger et al<sup>18</sup> treated 45 carriers of Group A hemolytic streptococci with 1 gm of sulfadiazine daily for four-day to fifty-day periods, with no development of sulfadiazine-resistant strains during the treatment period. So far as is known at present, no evidence of the development of resistant strains of hemolytic streptococci has been reported from any rheumatic fever patients who are receiving daily prophylactic treatment with sulfonamides.<sup>20</sup> Under the conditions of the studies cited above, no resistant strains of hemolytic streptococci developed.

The spread and epidemiologic problems that these resistant organisms presented in the armed forces have been summarized in previous reports.<sup>3-8, 16</sup> Although it was known that the civilian population was exposed to these resistant strains of hemolytic streptococci, no epidemics therefrom were reported until 1946, when an outbreak of Type 19 infections appeared in Cooperstown, New York.<sup>9</sup> Except for the Type 19 strains, resistant to 25 mg per 100 cc of sodium sulfadiazine, isolated during that study, none of the types showed any evidence of resistance. In the present report all strains, except the one resistant Type 19 strain, were susceptible to the action of sodium sulfadiazine. Apparently, there have been no problems of therapy in these resistant

streptococcal infections since they can be adequately treated with penicillin.<sup>21</sup>

The results of the present study of 167 strains of Group A hemolytic streptococci indicate that only one strain, which belonged to Type 19, was resistant to the action of sulfadiazine. This strain grew in a concentration of 25 mg of sodium sulfadiazine per 100 cc — the same concentration as the epidemic Type 19 strains that were prevalent in the armed forces. The source of this strain is not known, but it was probably introduced into this area by Army or Navy personnel. The possibility that this resistant strain is a naturally resistant variant cannot be ruled out, but the available information indicates that the resistant organism encountered in this study was the same as that in the armed forces.

The data of this study show that sulfonamide-resistant variants of Group A hemolytic streptococci did not arise in this area of Boston and its environs, where sulfonamides are used in the customary manner in the treatment of patients and where sulfonamide prophylaxis has not been widely employed.

From the accumulated evidence presented, it seems that conditions of mass sulfadiazine prophylaxis as they existed in the armed forces<sup>1, 2</sup> were conducive to the development of sulfadiazine-resistant strains of hemolytic streptococci. Regarding the conditions under which drug-resistant organisms can be expected to arise, one observer has postulated that "the infection shall be a common type providing very large numbers of micro-organisms within which a rare mutation has a chance to arise, and second — and this is the medically important point — that a large proportion of the potential hosts shall be treated with the drug in question."<sup>16</sup> To date these resistant strains have not presented any particular problem in civilian life and can be adequately treated by penicillin therapy. The possibility of the development of resistant strains of bacteria during large-scale mass prophylactic programs should be kept in mind, and such programs should be used only as an emergency measure.

## SUMMARY

Sulfonamide sensitivity determinations on 167 strains of Group A hemolytic streptococci, isolated from patients from Boston and surrounding suburbs, are presented. Only one strain, Type 19, was resistant to 25 mg per 100 cc of sodium sulfadiazine.

The pertinent literature regarding the development of sulfonamide-resistant hemolytic streptococci is reviewed.

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## MEDICAL PROGRESS

### THE ROLE OF PLEUROPNEUMONIA-LIKE ORGANISMS IN GENITOURINARY AND JOINT DISEASES (Concluded)\*

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THE high incidence of acute joint disease in male patients with positive prostatic cultures, in addition to the knowledge that animals infected with L organisms frequently have arthritis, suggests that pleuropneumonia-like organisms play a role in producing the joint disease in the patients. The hypothesis that this organism is the cause of the arthritis is somewhat supported by the fact that in 2 cases of Reiter's syndrome (as Case 11) L organisms were cultured from the knee-joint fluid. However, no L organisms were found in the synovial fluids in the other 11 cases in this series in which a search for these organisms was made.

In women, a relation between the presence of the L organism in the genital tract and the development of joint disease was not so apparent. Among 58 women yielding positive cultures in the original series, only 9 had joint complaints. One of these patients also had gonococci in the cervical cultures. Two other cases were arbitrarily introduced into the series since they had rheumatoid arthritis and formed part of a group of 12 female patients with

rheumatoid arthritis in whom routine examination of cervical cultures for L organisms was made. Five of the 6 remaining patients had bad swelling and pain of long duration in various joints. The other patient (Case 10) had an acute arthritis that had developed two weeks after marriage. Her husband (Case 9) also developed joint symptoms eight weeks after marriage, and L organisms were found in the prostate at that time. In view of the high incidence of L organisms in the female genital tract (26 per cent) and the relatively low percentage of joint disease in female patients with positive cultures, there is no definite evidence of a relation between the L organism and the joint disease in these cases. However, the observations in the married couple suggest not only that the joint involvement was related to the L organism but also that certain strains have a greater tendency than others to produce joint disease. Further suggestion of a possible relation between the L organism and joint disease in women was furnished by 2 other patients, seen since the original series was completed, who had acute arthritis at the time cervical cultures were positive for L organisms and negative for gonococci.

Until further information is available concerning the pathogenicity of the various human strains of pleuropneumonia-like organisms, it is difficult to conclude whether or not the conditions produced by these organisms are contagious. Certain findings suggest that they are. The wives of 5 of the men from whose prostates L organisms were cultured

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were studied, and in 2 cases *L* organisms were found in the cervical cultures. In 1 case—that of the married couple discussed above—both husband and wife developed acute arthritis soon after marriage. Beveridge, Campbell and Lind<sup>9</sup> cultured pleuropneumonia-like organisms from 3 of 11 women from whom men had contracted nonspecific urethritis. The fact that the genitourinary, joint or eye symptoms in at least 7 of the men with positive cultures in the present series developed within a few days after sexual exposure suggests that the disease is venereal in some cases. However, in many cases no history of exposure was obtained. The possibility that the gastrointestinal tract was the portal of entry in some cases is suggested by the fact that at least 6 patients had diarrhea just before or at the onset of the disease.

The treatment of diseases produced by pleuropneumonia-like organisms is still in an experimental stage. In rats and mice these diseases have been shown to be prevented or effectively treated in a high percentage of cases by gold compounds<sup>22, 23</sup> and by streptomycin.<sup>24</sup> Penicillin has not been effective in animals.<sup>25</sup> Pleuropneumonia-like organisms are not sensitive in vitro to sulfonamides or penicillin, but the growth of some strains has been found to be inhibited by streptomycin in a concentration of 20 microgm per cubic centimeter.<sup>17</sup> In the present series gold was used in only 1 patient (Case 4) and was ineffective. None of the patients treated with sulfonamides or penicillin showed any improvement in the genitourinary or joint symptoms. Streptomycin was used in 8 patients in whom the infection was limited to the genitourinary tract (see Cases 4 and 5), including 4 cases of cystitis, in 1 patient with acute arthritis associated with urethritis, and in 5 patients with Reiter's syndrome (Case 12).<sup>\*</sup> In 7 of the 8 cases of genitourinary-tract infection there was rapid disappearance of symptoms during treatment, and cultures became negative for *L* organisms. The eighth case, in a patient who had had urethritis for sixteen years (Case 4), showed only a transient improvement in symptoms, and the pleuropneumonia-like organisms did not disappear from the urethral cultures. In the patients with acute arthritis or Reiter's syndrome, there was improvement in symptoms during and immediately after treatment. However, evidence of joint inflammation persisted for weeks, and the sedimentation rates remained elevated. In none of the cases were *L* organisms cultured after treatment. Streptomycin therapy did not prevent recurrences of the disease in Case 12. The results of streptomycin therapy were not conclusive but indicate that the drug is probably effective in most cases of uncomplicated genitourinary-tract disease due to pleuropneumonia-like organisms. In Reiter's

syndrome the results were sufficiently suggestive to warrant further trial of this therapy.

### CASE REPORTS

The following brief abstracts include characteristic cases from the various groups.

**CASE 1 (M G H 22349) †** A 33-year-old female research worker who handled rats almost daily and who gave no history of previous genitourinary disease noted sudden onset of tenderness and swelling of the right labium majus 10 days after marriage. On examination an abscess of Bartholin's gland was found. Cervical smears were negative for gonococci. Excision of the abscess *in toto* was performed, and cultures were made at the operating table from the center of the abscess, which contained creamy-yellow pus. These cultures yielded an abundant growth of *L* organisms in pure culture. Streptobacilli or gonococci could not be demonstrated by smear or culture. The patient recovered uneventfully.

**CASE 2** An 18-year-old single girl noted the onset of profuse vaginal discharge 4 days after intercourse. On examination there was an acute vaginitis, with a fiery red mucosa and yellow purulent exudate. Cultures of this exudate yielded a pure growth of *L* organisms. Gonococci could not be demonstrated by smear or culture. The vaginitis cleared up within 1 week.

### Patients with Urethritis and Prostatitis

**CASE 3** A young married man, 36 hours after extramarital exposure, observed slight urethral discharge. On examination no discharge was apparent, but the prostate was found to be swollen and painful. In the culture made from a sample of urine immediately after prostatic massage many *L* colonies but no gonococci were seen. A second culture 10 days later was negative for *L* organisms and for gonococci. The subsequent clinical course is not known.<sup>‡</sup>

**CASE 4 (M G H 492207)** A 35-year-old married man was admitted to the hospital because of persistent urethral discharge. Sixteen years previously, 3 days after intercourse, he had developed a yellowish urethral discharge and inguinal lymphadenopathy. The discharge had not changed throughout the 16 years despite many types of treatment, including sulfonamides, penicillin and numerous kinds of local therapy. Cultures had always been negative for gonococci, but during the year before admission had been positive for pleuropneumonia-like organisms on several occasions. Examination was negative except for slight urethral discharge and enlargement of the prostate. The patient was treated with streptomycin, in a dosage of 4 gm a day, for 1 week. The discharge disappeared after 1 day of treatment, but cultures of the prostatic secretion continued to show many colonies of *L* organisms. Ten days after treatment was stopped the discharge returned and has persisted for the past 11 months. During this interval he has been treated with myocrisine, receiving 325 mg in 5 weeks without effect.

### Patients with Cystitis

**CASE 5 (M G H 532255) §** A 26-year-old single man was admitted to the hospital because of frequency of urination and terminal hematuria. Three years before admission he had had urethral discharge and frequency of urination lasting for several weeks. Subsequently, there had been repeated recurrences of burning and frequency. Two weeks before admission he had first noted blood in the terminal portion of the urine. Cultures had always been negative for gonococci. Examination was negative except for the fact that the prostate was rather soft. The urine was loaded

\*We are indebted to the Committee on Chemotherapeutics of the National Research Council for the streptomycin used during most of this study and to Merck and Company for the streptomycin now being employed for test of its efficacy in the treatment of infections due to pleuropneumonia-like organisms.

†We are indebted to Dr. L. Parsons, of the Massachusetts General Hospital for permission to report this case. Reference to this patient has been made by Dienes and Edsall.<sup>2</sup>

‡This was a patient of the late Dr. Richard F. O'Neil.  
§We are indebted to Dr. Fletcher H. Colby, of the Massachusetts General Hospital, for permission to include this case which has also been reported by Kane and Foley.<sup>26</sup>

with erythrocytes and leukocytes. Three routine cultures of urine showed no growth but cultures on boiled blood ascitic agar contained numerous colonies of pleuropneumonia-like organisms. The patient was given 2 gm of streptomycin daily for 4 days and 1 gm daily for the following 5 days. Cultures became negative for L organisms after 3 days of treatment, and the urinary sediment showed only rare cells. There has been no recurrence of symptoms in the subsequent 14 months.

### *Patients with Chronic Arthritis*

**CASE 6 (M G H 534532).** A 32-year-old married man was admitted to the hospital because of severe pain and redness of the right eye of 1 week's duration. Seven years before admission he had had a nrethral discharge, smears from which were reported to contain gonococci. Five years later he had begun to notice migratory pains in the hips, right knee, neck, and lower back. Six months before admission the right knee became swollen and painful. Examination showed an iritis of the right eye with marked chorioretinitis, an effusion in the right knee and slight tenderness and induration of the prostate. Prostatic cultures showed a moderate growth of L organisms and of non-hemolytic streptococci. The arthritis subsided in 3 months but the iritis still persists at the end of 11 months. During this period central chorioiditis has developed and has been treated with fever induced by intravenous injection of typhoid vaccine. Prostatic cultures have remained positive for L organisms.

It is impossible to determine whether or not the various features of this patient's disease are interrelated in any way.

### *Patients with Acute Arthritis without Eye Involvement*

**CASE 7 (M G H 352561).** A 47-year-old married man noted burning on urination 2 or 3 days after sexual exposure. One week later he developed stiffness of the knees, right wrist and right shoulder. The stiffness of the knees persisted and 3 weeks later the left wrist became very swollen, red, hot and tender. These symptoms subsided in 2 or 3 days but the right wrist became involved. Examination on the following day showed tenderness, increased heat and pitting edema of the right wrist and the dorsum of the right hand and a moderate-sized effusion in the left knee which was warm and tender. The prostate was tender and boggy. Culture of the prostatic secretion showed numerous colonies of L organisms and *Staphylococcus aureus* but was negative for gonococci. All symptoms subsided in 2 weeks though the sedimentation rate remained elevated. There was no recurrence of symptoms during the subsequent 2 years.

**CASE 8 (M G H 315068).** A 29-year-old single man had had a urethral discharge 6 months before admission. Soon thereafter he had noted pain and swelling of the left knee, left third toe and right third finger. There had been no response to sulfonamide therapy but the symptoms subsided slowly over the course of 4 months. Two weeks before admission the nrethral discharge recurred and pain developed in the right hip, left shoulder and tarsometatarsal joints on both sides. The patient had had a urethritis said to be of gonococcal origin, 8 years before admission. On examination at the time of admission the left knee contained a moderate-sized effusion and was tender. The prostate was large and boggy. Cultures of prostatic secretion showed abundant L colonies but no gonococci. The patient was again treated with sulfonamides with no effect. The symptoms gradually disappeared over the course of 2 months. Cultures of prostatic secretion were negative for L organisms 4 years later.

**CASE 9 (M G H 291517).** This 38-year-old man the husband of the patient in Case 10 was seen in 1942, when he had been married 8 weeks. He had had urethritis in 1929 and again in 1934. Gonococci were said to have been seen in smears during both these attacks, but they could never be demonstrated at any time thereafter. In 1937, 1940 and 1941 he had been treated for chronic prostatitis smears showing pus cells but no gonococci. In March 1942 the patient was admitted to the hospital for painful swelling of the left wrist of 3 days duration. On examination the prostate did not feel abnormal but massage yielded fluid containing 20

30 pus cells per high-power field. Cultures yielded no gonococci but gave an abundant growth of L organisms streptococci and diphtheroids. Four months later pain and swelling developed in the right elbow, persisting for 9 months. During this episode the prostate was found to be boggy and the vesicles were tender. Prostatic cultures yielded occasional L organisms and an abundant growth of bacteroides nonhemolytic streptococci and *Staph. albus*. Four years later the patient had recurrent attacks of pain in the left flank, and x-ray study showed a stone in the lower end of the left ureter. At the time of admission for removal of the stone the urine was cultured but showed no growth of pleuropneumonia-like or other organisms.

**CASE 10 (M G H 348216).** A 30-year-old woman, the wife of the patient in Case 9, was admitted to the hospital in March, 1942, 3 days after her husband's first admission. She gave no history of genitourinary disease and had been well until 6 weeks before entry when 2 weeks after marriage she developed stiff swollen knees. There was no redness or heat about the knees and the swelling caused only moderate discomfort. No other joints were involved and there was no fever and no constitutional symptoms. Pelvic examination revealed a slight cervical discharge, cultures of which yielded a pure growth of L organisms. No organisms were found in gram-stained or Giemsa-stained films of the joint fluid, and none could be recovered in culture. The patient was discharged unimproved after 1 week. The involvement of the knees gradually subsided during the following year.

### *Patients with Acute Arthritis with Eye Involvement (Reiter's Syndrome)*

**CASE 11 (M G H 440804)\*.** A 26-year-old single man developed a purulent urethral discharge 36 hours after sexual exposure. He was treated with sulfathiazole and sulfadiazine, but the discharge persisted and 3 weeks after onset he noted burning, frequency, urgency and terminal hematuria. Approximately 5 weeks later bilateral conjunctivitis appeared and within a few days he complained of pain in the lumbosacral region as well as pain and swelling of the right ankle, right shoulder, left elbow and left knee. On examination 3 days later, the temperature was 100.4°F with slight conjunctival injection and swelling and tenderness of the right ankle, left knee and right sternoclavicular joint. The nrethral discharge had subsided but a catheterized specimen of urine was loaded with white cells. Cultures of the urine and prostatic secretion showed an abundant growth of L organisms and a few colonies of staphylococci but were negative for gonococci. Two colonies of L organisms were found in the culture of fluid from the left knee. At the time of discharge, cultures of the urine showed only a few L organisms. The patient was treated with 120,000 units of penicillin with out effect but all symptoms subsided slowly during the course of 2 months.

**CASE 12 (M G H 255127).** A 26-year-old single man had had pain in the right ankle and right knee and slight urethral discharge for 2½ weeks before admission. Examination revealed marked swelling of the right knee with an effusion and moderate swelling of the right ankle. The prostate was slightly enlarged and boggy. Three weeks later an iritis developed in the left eye. Culture of the prostatic secretion showed abundant growth of L organisms and many streptococci and colon bacilli but was negative for gonococci. The patient was treated with sulfathiazole and penicillin without effect. The symptoms gradually subsided during the course of 6 months. He had had a similar attack 4 years previously with bilateral conjunctivitis and keratitis, purulent urethral discharge and arthritis. There had been a second attack 1 year later, manifested by urethral discharge, balanitis and prostatic bilateral conjunctivitis and keratitis and arthritis.

After the third attack described above had subsided the patient remained entirely well except for occasional episodes of slight conjunctivitis until 1 year after discharge when prostatic massage was performed. Culture of the prostatic

\*We are indebted to Dr. Fletcher H. Colby of the Massachusetts General Hospital, for permission to report this case, the first urinary secretion of which have been reported by him.

†These first two attacks have been reported elsewhere.



secretion was negative for L organisms. Two days later, he noted slight urethral discharge and 1 week later developed bilateral conjunctivitis. During the following week, the right hip and both knees became painful. On examination the conjunctivas of both eyes were markedly inflamed. The right hip was painful, and both knees contained effusions. Prostatic cultures showed an abundant growth of L organisms and a few staphylococci but no gonococci. The urethritis and conjunctivitis subsided in 2 weeks, but during the following 2 months, he continued to have intermittent attacks of pain, swelling and tenderness of wrists, knees and left first metacarpophalangeal joint. Roentgenograms showed moderate decalcification of the bones around the knees and wrists. At the end of 2 months, streptomycin was obtained, and the patient received 21.5 gm. in 6 days. Subsequently, he had no further recurrence of joint symptoms though the sedimentation rate remained slightly elevated for 3 months.

Thereafter, he continued to feel well until 3 months later, when he noted stiffness and swelling of the left knee. Four days later there was recurrence of slight urethral discharge and on the following day slight conjunctivitis. On examination 5 days later, the left knee and the interphalangeal joint of the right first toe were hot, red, very painful and swollen. There was a severe conjunctivitis, with purulent discharge, and a slight urethral discharge. Cultures of the urethral discharge and of the urine showed a moderate growth of L organisms and a few colon bacilli and *Staph. albus* and *Staph. aureus*. Roentgenograms showed persistence of slight decalcification of the bones around the knees. The patient was treated with streptomycin in a dosage of 4 gm. a day for 13 days. The urethritis and conjunctivitis subsided within 1 week, but swelling of the left knee persisted for 2 months. The sedimentation rate has remained slightly elevated for the past 5 months.

### DISCUSSION

The observation that human beings may harbor organisms belonging to a group that includes several important animal pathogens is in itself interesting. Interest is heightened by the fact that these pleuropneumonia-like organisms appear to be pathogenic to human beings. The most definite indication of pathogenicity has been obtained from the study of male patients. The fact that all the patients in this series had urethritis, prostatitis or cystitis suggests that the organism is pathogenic for the genitourinary tract. Most impressive were the patients with cystitis, such as Case 11, in whom the L organisms were present in pure culture for a long period and decreased markedly or disappeared from the urine as the clinical symptoms subsided. Further indication of the pathogenicity was obtained from one of the patients with Reiter's syndrome (Case 12). L organisms were cultured from the prostatic secretion at the onset of three separate attacks of the disease and were not found in the interval between the episodes.

The presence of acute joint involvement in 27 of the 58 men with positive cultures for L organisms suggests pathogenicity for synovial tissues as well as the genitourinary tract. In 2 patients with Reiter's syndrome, organisms were cultured from the synovial fluid. This association with joint disease is of particular interest because joint involvement is a common feature of the diseases produced by the pleuropneumonia group of organisms in animals.

The evidence of pathogenicity gained from the study of female patients is more equivocal. The relatively high incidence of L organisms in the

female genitourinary tract suggests that they are part of the normal bacterial flora in this location. On the other hand, their presence in various inflammatory processes of the genitourinary tract either in pure culture or in much greater abundance than other bacteria suggests that they are at times pathogenic.

In evaluation of the evidence gathered to date it should be remembered that some strains are presumably not recovered by the present methods, and that the strains isolated probably belong to more than one species and differ in their pathological significance. The fundamental biologic study of the organism obtained from human beings is still in a primitive stage. The cultural methods, which at present are the only means of recognition, are probably inadequate. Attempts are now being made to develop biologic methods, such as serologic and skin tests. The need for a more detailed study of the properties of the various strains, especially their serologic characteristics and their pathogenicity, is indicated by the observations that attest to their ability to cause disease in human beings.

Further difficulty in evaluating the role of pleuropneumonia-like organisms arises from the fact that some of the bacteria commonly found in human beings grow in an L variant form under certain cultural conditions, as in the presence of penicillin. Because of this difficulty, the 8 male patients with severe urinary-tract infection in whom L organisms were found only after the growth of other bacteria was suppressed either by addition of penicillin to the medium or by treatment of the patient with penicillin or streptomycin have not been included in the present series. It is impossible to assess the significance of the L organisms in these cases. It seems probable that they represent one of the many organisms that together cause the urinary-tract infection. However, they may be variant forms of the other bacteria present in the inflamed urinary tract.

### SUMMARY

The properties of pleuropneumonia-like organisms (L organisms) and the methods used for their isolation and identification are briefly described.

Pleuropneumonia-like organisms were present in 58 of 222 routine specimens (26 per cent) from the uterine cervix and vagina and may be part of the normal bacterial flora in these locations. Suggestion of possible pathogenicity, however, was provided by their recovery from inflammatory processes of the female genital tract.

Pleuropneumonia-like organisms were found in only 6 of 71 routine specimens from the male genitourinary tract. Evidence of their pathogenicity was more definite than that in women, since all 58 patients of this series from whom positive cultures were obtained had urethritis, prostatitis or cystitis. In 6 of the 9 cases in which the

infection extended into the bladder the organisms were obtained in pure culture from the urine. Gonococci and L organisms were found simultaneously in only 2 male patients.

Material from other sources, including the respiratory and gastrointestinal tracts and cerebrospinal fluid, was examined by similar methods but with negative results except in synovial fluids from 2 patients with Reiter's syndrome.

Eighteen of the 58 male patients with genitourinary-tract infections had an acute type of arthritis when the cultures were positive for L organisms. Nine of these men had simultaneous urethritis, conjunctivitis and arthritis, the syndrome characteristic of so-called Reiter's disease. In 1 patient L organisms were found in the prostate during three attacks of the disease.

These observations indicate that pleuropneumonia-like organisms have pathogenic activity in the genitourinary tracts of men and women and may be related etiologically to an acute infectious type of arthritis and to Reiter's syndrome.

We are indebted to the following physicians for permission to include cases in this series: Drs. F. Albright, J. D. Barney,

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Eight of the cases of this series have been included in other papers.<sup>2, 3, 7, 8, 9, 10</sup> Seven others will be reported by Berg and McLaughlin.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., Editor

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### CASE 34161

#### PRESENTATION OF CASE

A three-and-a-half-month-old male infant entered the hospital because of persistent diarrhea.

The birth weight was 6 pounds, 3 ounces, and a statement was made that the baby was blue at birth. However, he gained weight at a normal rate, ate well, and seemed normal in every way except that when he cried or breathed rapidly some cyanosis appeared. There had never been any convulsions, hematuria, vomiting or jaundice.

Four weeks prior to entry the patient developed a cough and coryza, and had several bouts of what were said to be projectile vomiting. Four days later he was taken to another hospital, where a diagnosis of bronchopneumonia was made. X-ray films at that time showed the heart to be to the right of the sternum and an additional diagnosis of congenital heart disease was made. He remained in the hospital and ten days before admission to this hospital

he developed a persistent and moderately severe diarrhea (ten to twelve bowel movements per day). Several of the other infants on this ward also developed diarrhea at about the same time. Five days before admission the diarrhea became much severer, and penicillin therapy was started. Because of the persistent diarrhea the patient was transferred to this hospital.

Physical examination revealed a marasmic and cyanotic infant. He appeared to be fairly well hydrated. Cyanosis was present to a mild degree but was considerably intensified when the patient cried. The chest was clear to percussion and auscultation. The heart was percussed to the right of the sternum and the point of maximum impulse was in the fifth interspace 4 cm. to the right of the sternum. The rhythm was normal, and the rate was 140. There was a soft, Grade II systolic murmur heard best in the third interspace to the left of the sternum.

Examination of the blood disclosed a red-cell count of 4,740,000, with a hemoglobin of 14 gm., and a white-cell count of 7500, with 88 per cent neutrophils. The urine was normal. Blood cultures were negative, and cultures of the stool showed no significant organisms. A blood Hinton test was negative. A tuberculin test in a dilution of 1:1000 was negative.

Soon after admission the number of daily bowel movements decreased markedly, until they became normal. On the third hospital day the child had an episode of severe cyanosis associated with vigorous respiratory activity. The trachea was suctioned, and much thick white mucus was recovered. The patient recovered entirely within fifteen minutes.

The next day a swallow of lipiodol was given, and x-ray examinations showed no evidence of an esophagotracheal communication. The lipiodol passed down the esophagus into the stomach, which lay in normal position on the left side. There was no evidence of constriction of the esophagus. There was a slight indentation opposite the arch of the aorta, which seemed to indicate that the aorta descended on the left side. There was also a ques-



FIGURE 1 *Roentgenogram, Showing the Apex of the Heart in the Right Midclavicular Line*

tionable filling defect just above the aortic arch as seen on the anteroposterior view. The lung fields were essentially clear, without evidence of active disease. The pulmonary vascular markings throughout seemed to be decreased. The apex of the heart lay in the right midclavicular line (Fig. 1).

On the sixth hospital day the patient had a cyanotic episode, much the same as the previous one. However, suction did not relieve the attack, and a laryngoscope and then a bronchoscope were passed and a small amount of mucus was removed. After oxygen had been administered for some time the patient was able to breathe somewhat more easily, but there was still considerable forcefulness to the respiratory movements and some retraction of the interspaces. Because of the presence of bubbling rales at the lung bases sulfadiazine and penicillin therapy were instituted. An electrocardiogram was interpreted as being consistent with dextrocardia. The spinal fluid was not remarkable. Bilateral sub-

dural taps were done on the eighth day, without return of fluid. On the fourteenth day the temperature began to spike up to 102°F. The white-cell count was 10,900. Physical examination showed a questionable decrease in the percussion note over the left lower lobe. Because he was not taking his feedings very well, the patient had been started on stomach-tube feedings. On the twentieth hospital day, immediately after one feeding, he began to cough, became cyanotic, breathed very rapidly, and died, despite attempts at suction and artificial respiration.

#### DIFFERENTIAL DIAGNOSIS

DR FRANCIS McDONALD Will Dr Wyman please demonstrate the films?

DR STANLEY M WYMAN The best demonstration of the esophagus is shown by the opaque tube, which extends through the esophagus into the stomach on the right side. The heart is seen on the right.

DR McDONALD "There was a slight indentation opposite the arch of the aorta, which seemed to indicate that the aorta descended on the left side."

DR WYMAN That is suggested on one of the spot films. However, a better look at the plain film with the tube in place shows a considerable shadow to the right of the esophagus and trachea, which makes me think that the aorta actually descends on the right side rather than on the left. I think that the observation of the left-sided aorta is perhaps inaccurate. The filling defect I cannot identify. There is good filling of the esophagus in this portion. I can detect no true abnormality from the films, which are not satisfactory and are noncontributory. The chest films show that the heart is in the right side of the chest, with the apex pointing to the right. The heart is not grossly enlarged. The pulmonary-vascular shadows are decreased in prominence. There is some multiple increased density in the left lung field medially. I should think that this was some sort of pneumonic process. It is seen on the other films consistently. We can therefore say that the heart is not grossly enlarged and lies on the right side (a dextroposed heart), the pulmonary vascular shadows are decreased in prominence and there is presumably some congenital anomaly.

DR RONALD C SNIFFEN The liver is on the right side?

DR WYMAN Yes, it is on the correct side.

DR McDONALD Was the mucus removed by the bronchoscope cultured?

DR CHARLES U LOWE It was cultured and yielded *Staphylococcus aureus*.

DR McDONALD I would welcome expert advice on the electrocardiogram.

DR SNIFFEN I do not believe there is anyone here who can give it.

DR McDONALD It sounds like a relatively clear-cut interpretation. About the only mistake that might be made is transposition of the arm electrodes.

I am not a cardiac expert, so that for the interest of the group, I shall quote from Taussig's\* book.

Lead I is in the mirror image of normal. Leads II and III replace each other. In Lead I both P waves and the T waves are normally inverted and the principal deflection of the QRS complex is downward. The findings in Lead III are those usually seen in Lead II and the form of deflection in Lead II is similar to that seen normally in Lead III.

DR. SNIFFEN The interpretation of the electrocardiogram was as follows: "The tracing is consistent with dextrocardia and inverted Lead I and interchanged electrodes 2 and 3 give normal axis and T waves."

I might say that the child did much better in an oxygen tent than is indicated in the record.

DR. McDONALD It seems as if we have two main categories for diagnosis here. One is infection. We have an infant in an age group that is immunologically immature, subject to invasion by colon bacilli, staphylococci, influenza bacilli and other organisms, in addition to the usual streptococcal and pneumococcal invaders of the respiratory tract. It is extremely important in this age group to obtain blood cultures (using pour plates and broth flasks) and cultures of coughed-up secretions to obtain a precise idea what the organism is and to govern therapy accordingly. This patient was given sulfadiazine and penicillin, probably on that basis. *Staph. aureus* was obtained on one attempt and cannot be passed off as a contaminating organism, as it frequently may in an adult group. *Staphylococcus* may be an invading agent in this age group. The cough, the dyspnea, the course and the x-ray findings, which might possibly be consistent with an early atelectasis or bronchiectasis as well as pneumonia, make me conclude that the baby did have pneumonia. The second diagnosis is a definitely proved cardiac abnormality. I believe that we can take the word of Dr. Wyman that displacement of the heart was not likely from any of the physical findings or x-ray evidence. The electrocardiogram of dextrocardia is a conclusive finding. The presence of dextrocardia without situs inversus markedly increases the likelihood of associated anomalies. We can therefore assume that, in addition to the dextrocardia, either there were anomalies of the heart itself or, if by chance the aortic arch was on the left side, there was a good likelihood of anomalies of the vessels at the base of the heart. As may be seen in this case, the heart is twisted around, with the aortic arch where it should be normally, with the corresponding difficulty in readjustment of the vessels at the base. In addition to the diagnosis of dextrocardia without situs inversus I shall say question of pulmonary stenosis, question of single ventricle and question of anomaly of vessels at the base of the heart.

DR. SNIFFEN You took care of this patient, Dr. Lowe. Have you anything to add?

DR. LOWE There are two things that might be clarified—first of all the difficulties with inspiration, the cyanosis usually followed feeding, which strongly suggested vascular anomaly at the base of the heart. The second point is that it was obvious that oxygen helped the child, which is unusual in children with cyanotic heart disease.

DR. RICHARD SCHATZKI Is it not likely if a baby is short of breath that feeding usually makes the difficulty worse?

DR. LOWE The child was not short of breath normally. The extreme attacks described in the record

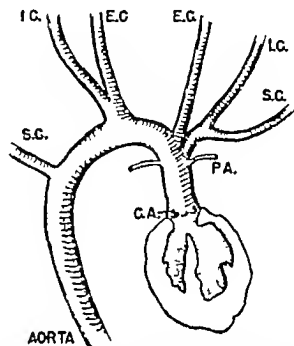


FIGURE 2. Drawing of the Heart and Great Vessels, Showing Persistent Truncus, Patent Interventricular Septum, Tricuspid Semilunar Valve, Pulmonary Arteries from Truncus, Persistent Fifth Aortic Arch on the Left and Right Sided Aorta.

occurred seven times while the child was in the hospital, and the last one was fatal. Dyspnea was not part of the general picture.

#### CLINICAL DIAGNOSES

Asphyxiation due to aspiration of feeding  
Persistent double aortic arch  
Dextrocardia  
Pneumonia  
Congenital heart disease

#### DR. McDONALD'S DIAGNOSES

Pneumonia  
Dextrocardia  
? Single ventricle.  
? Pulmonary stenosis  
? Anomaly of vessels at base of heart

#### ANATOMICAL DIAGNOSES

Right-sided aorta  
Persistent truncus arteriosus  
Patent interventricular septum  
Persistent fifth aortic arch on left  
Acute purulent bronchitis with early bronchopneumonia

\*Taussig, H. B. *Congenital Malformations of the Heart*, 618 pp. New York: Commonwealth Fund, 1947.

## PATHOLOGICAL DISCUSSION

DR SNIFFEN At the time of death the patient was somewhat emaciated and cyanotic. The abnormal findings were confined to the heart and lungs. In the lungs there was a generalized purulent bronchitis most marked in the left lower lobe. This was accompanied by a mild peribronchial inflammatory infiltration involving the alveolar walls and septums. On the left side there was a fibrinous and fibrous pleurisy without effusion. A small amount of mucus and aspirated gastric contents were found in the trachea and major bronchi. The apex of the heart lay in the right midclavicular line. The pericardium and myocardium were normal,

arteries, which were not over 1 mm in diameter. The ductus arteriosus was not patent. Then, as one proceeded distally along the arch of the aorta, just beyond the left pulmonary vessel, an arterial trunk left the aorta. This trunk divided immediately into two branches, the first giving rise to the left subclavian and internal carotid arteries, and the second to the left external carotid artery. The next aortic branch was the right common carotid artery, with its external and internal divisions, and the last major vessel to leave the aortic arch was the right subclavian artery.

We believe that these structural abnormalities were the results of the disintegration of the first

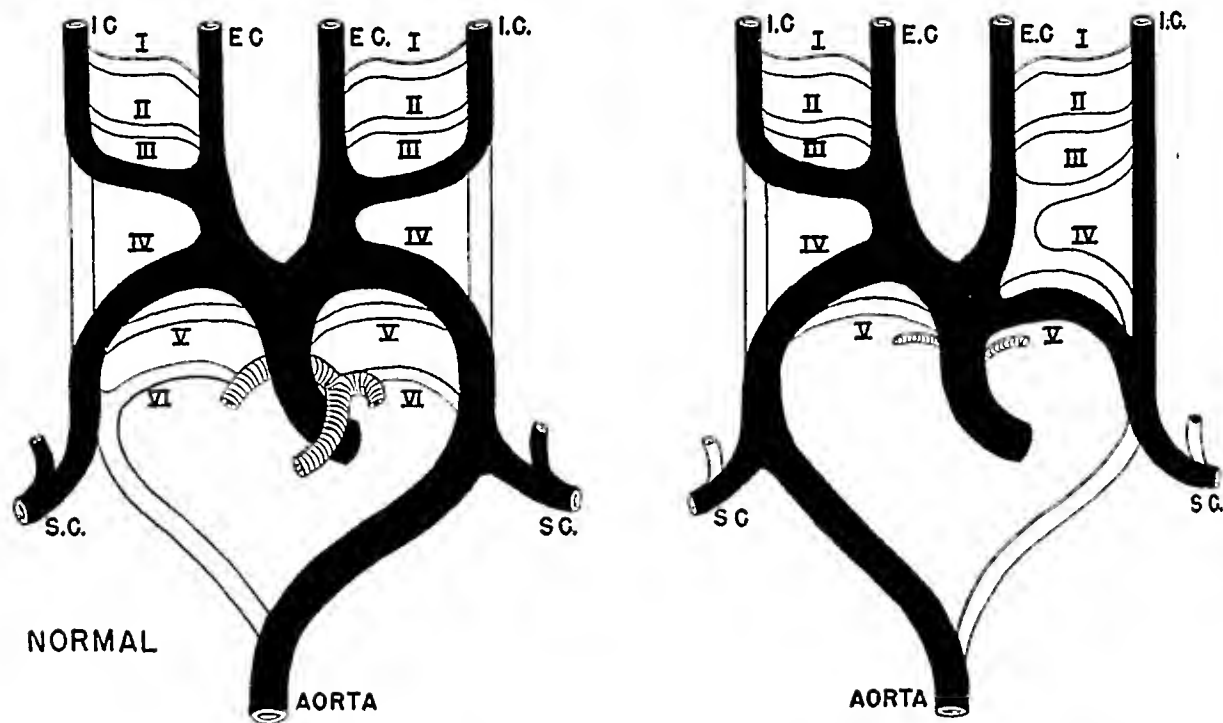


FIGURE 3 Drawing, Showing Disintegration of the First Four Aortic Arches on the Left, with Persistence of the Fifth Aortic Arch

the latter measuring 4 mm in each ventricle. The heart was slightly enlarged.

The dissection of maldeveloped hearts is confusing, since minor structural variations change the interpretation of the developmental abnormalities a great deal. I shall demonstrate several diagrams so that I will not become snarled in the mechanics of the arterial abnormalities.

The first is a drawing of the heart and great vessels in this child (Fig 2). The heart showed a persistent truncus, and as might have been expected with this anomaly, there was a defect in the membranous septum between the ventricles. The truncus overlay both ventricular chambers, but mainly the right ventricle. The outlet was guarded by three normal semilunar valve cusps of equal size. The coronary vessels followed the usual course. There was a right-sided aorta. The first branches to arise from the truncus were two minute pulmonary

four aortic arches on the left side, with persistence of the fifth aortic arch (Fig 3). The reason for this opinion is the fact that the main trunk on the left side was very short. If it were long, we could be confident that the fourth arch had persisted after the disintegration of the first three arches. Furthermore, this main trunk arose immediately distal to the left pulmonary artery. On the right side the fourth arch and dorsal aorta had persisted to form the main arterial trunk.

The formation of three equal semilunar cusps in the truncus is difficult to understand. One would expect four cusps of equal size or unequal size or three unequal cusps. In fact the truncus had the structure of a normal aorta.

As a sidelight, the left lung was divided into three lobes, and the right lung had only two lobes.

No constrictions were found in the esophagus, and the abdominal organs were in the normal position.

## CASE 34162

## PRESENTATION OF CASE

A forty-eight-year-old chauffeur entered the hospital because of pain in the right elbow.

One year before entry the patient had a painful right upper arm for a few weeks following a strain in breaking a fall. He recovered completely from this episode, however, and remained asymptomatic until one month before entry, when he slipped and twisted the right arm while shoveling snow. He immediately sustained severe pain around the elbow, with radiation to the outer aspect of the right shoulder. The pain gradually subsided and disappeared a week later, when he first noted swelling of the "muscles" just above the elbow. Two weeks before entry physical examination and x-ray studies demonstrated a "tumor" of the lower humerus. One week later he slipped and fell and felt a crack in the arm, with resulting severe pain. X-ray films were taken, the arm was splinted, and he was sent to this hospital.

His father had died of carcinoma of the liver, and an uncle had carcinoma of the stomach.

The patient allegedly had enjoyed excellent health and denied weight loss, systemic symptoms, previous trauma or bone disease.

Physical examination revealed a well developed and well nourished man with moderate pitting edema below the lower third of the humerus, a swelling around the elbow and a soft-tissue mass, 2.5 by 5 cm., above the medial epicondyle, in the region of which there seemed to be some abnormal mobility. There was no discoloration of the skin and no evidence of motor or sensory impairment. A few firm, nontender lymph nodes (0.5 to 1.0 cm in diameter) were palpated bilaterally in the groin. No abdominal masses or chest abnormalities were demonstrated.

The temperature was 98°F, the pulse 76, and the respirations 15.

Examination of the blood showed a hemoglobin of 15.1 gm per 100 cc and a white-cell count of 11,400, with 79 per cent neutrophils. Urinalysis was negative. No Bence-Jones protein was found.

X-ray films of the right humerus demonstrated a destructive process 10 cm long in the distal third through the entire thickness of bone but with no spicule formation, no new-bone formation, and no periosteal elevation, there was a pathologic fracture through this area. The medulla above the lesion had some irregular areas of mottling, and the cortex appeared roughened (Fig 1). Scout films of the chest, spine, pelvis, left arm and both legs were normal.

An operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR CLIFFORD C. FRANSEEN. In the differential diagnosis of any suspected bone tumor, Dr Channing Simmons has taught us to review the history and

the signs and symptoms from three aspects: infectious, metabolic and neoplastic. The age (forty-eight years) is important to consider, as it is in any case of suspected bone tumor, and I shall deal with this later. This man either led a precarious existence or was very clumsy, because he suffered so many injuries from falls. Possibly, a neurologic examination would have thrown some light, but we do not have this information.

Let us consider infectious lesions first. With respect to osteomyelitis, the temperature was normal, and there was no suggestion of local inflammation. The record does not suggest a chronic inflam-



FIGURE 1

matory lesion, such as Brodie's abscess, especially by x-ray study. There was a slight elevation of the white-cell count, but little else to suggest that this process had arisen on the basis of osteomyelitis. In the latter lesions, also, enough reactive new-bone formation usually accompanies the osteomyelitis so that pathologic fracture is uncommon.

Syphilis must be considered only because it can simulate practically any bone lesion. The blood Hinton test is not given. We do not know whether or not it was taken, but, of course, it should be included in any study of a bone lesion. Syphilis, as a rule, produces considerable periosteal reaction, which was minimal or absent in this case. Tuberculosis can only be mentioned—we cannot rule it in or out in this case except for the statistical rarity of an isolated lesion in the humerus, especially since the chest film was normal.

We must consider the neoplastic group of diagnoses more seriously. The character of the destruction suggests that this was a neoplastic lesion, and probably a malignant one. Benign tumors that should first be considered are lesions such as bone cysts. They usually occur in the young age groups, and usually the first knowledge of their presence is the occurrence of pathologic fracture, unless they are picked up incidentally by an x-ray examination. It would be unusual for a man of this age to have one. A giant-cell tumor may remotely be suggested by the x-ray film, but the site in the bone is not a usual one. Perhaps we should see the x-ray films, since their interpretation becomes more important from now on.

DR STANLEY M. WYMAN: The lesion described lies in the lower third of the humerus (Fig 1) but does not extend down to the condyles. It seems to be a purely destructive process. There is no visible new-bone formation and no evidence of periosteal reaction. The roughening of the cortex is seen on either side of the shaft, much higher on the humerus. The spine, both femurs and the bones of the pelvis and lumbar spine show no definite disease. The lung fields are clear, the heart is not remarkable. I cannot make any statement about the abdominal viscera. The film is not of diagnostic quality.

DR FRANSEEN: Is the mottling in the center merely an area of irregular bone destruction, with no evidence of trabeculation?

DR WYMAN: I interpret the mottling as bone destruction, with residual areas of medullary trabeculation and some areas of residual cortex remaining between the areas of destruction. I think the process may have started centrally and extended to involve the entire thickness of the bone.

DR FRANSEEN: The x-ray appearance is different from what I had visualized from the written description. I did not appreciate that the periosteal reaction was so far away from the main lesion.

To continue the discussion, I can say that I am not familiar with any giant-cell tumor that has taken on an appearance such as this even when a pathologic fracture has occurred through it. If we, then, go on to consider other primary malignant tumors, Ewing tumor must be thought of. In this respect, again, the age of the patient is very important. I know of no case of Ewing tumor in this age group, but as in any bone lesions, it can perhaps occur. I met Dr Simmons just before this conference and asked him if he remembered any patient with Ewing tumor in this man's age group, but he could remember none. Geschickter and Copeland\* have reported no case in a patient so old as this man. We have all seen bizarre x-ray pictures in Ewing tumor, but there is no suggestion here of lamination of the periosteum or the other signs that are usually

associated with this tumor. As you perhaps know, at least 50 per cent occur in adolescence, with tapering off of the age incidence at either end. The tumor rarely occurs in the thirties. Age in itself is a strong argument against a Ewing tumor in this case, but, again, one cannot exclude it entirely.

Multiple myeloma should be considered, but this patient at forty-eight is not too good a candidate for it. This lesion is not the purely destructive lesion by x-ray study that one usually associates with multiple myeloma, and to have an isolated lesion in an extremity without evidence elsewhere would be extraordinary in multiple myeloma. In this disease the serum protein is sometimes elevated, but we do not have this determination to help us. The character of the patient's pain, which showed remissions between aggravations by trauma, is suggestive of multiple myeloma in a general way, but these are about the only facts I can find in its favor. There was no Bence-Jones protein in the urine and no evidence of nephritis on urinalysis, the latter frequently accompany the lesion. So much for multiple myeloma.

Considering other malignant bone tumors, malignant tumors of cartilaginous origin usually show some trabeculation, and this lesion, according to the x-ray interpretation, gave no suggestion of trabeculation, but rather irregular mottled areas of destruction. The osteolytic form of osteogenic sarcoma must more seriously be considered in a destructive lesion such as this appeared to be. There was not enough new-bone formation to consider the osteoblastic form of osteogenic sarcoma. The osteolytic form can begin subcortically and, as it gets larger, extend to a more central position, as in this case. Pathologic fracture, as in this case, is common. However, osteogenic sarcoma, as Dr Simmons has pointed out so frequently, is uncommon at this age unless associated with Paget's disease. However, there is some overlapping of age groups, and osteolytic sarcoma cannot be excluded on the basis of age alone. Reticulum-cell sarcoma must also be considered, and I would be unable definitely to exclude this lesion without a biopsy. I see no reason to consider other bone-destructive lesions such as eosinophilic granuloma. I have had no personal experience with them, but know that they usually occur in much younger age groups, particularly in children.

In the neoplastic group, we are then left to consider secondary or metastatic lesions of bone. A secondary lesion of Hodgkin's disease taking this form, without any other evidence of it elsewhere, would be very uncommon because bone involvement of this type would usually occur only in late stages of the disease. I think we can disregard the lymph nodes described in the groins, because, in my experience, nodes of this description can be felt in almost any person, so that I see no reason for considering Hodgkin's disease seriously.

\*Geschickter, C. F., and Copeland, M. M. *Tumors of Bone*. 709 pp. New York: American Journal of Cancer, 1931. P. 640.

I think, however, that metastatic carcinoma must be considered very seriously, since the picture is entirely consistent with that diagnosis. In a woman, the breast would, of course, be regarded as a primary source, but this man's breast was presumably easily examined, and a carcinoma would have been discovered if present. The most common sources to consider in this case are the prostate and kidneys. Metastases from prostatic carcinoma are apt to show more osteoblastic activity than this lesion did, but some that we have seen have been almost completely osteolytic. An isolated metastasis like this in an extremity is uncommon in carcinoma of the prostate. Renal-cell carcinoma frequently produces a soft, pulsating tumor. In this case there is no description of the consistence of the tumor. The few that I have seen have been confined especially to the sternum and upper end of the humerus. This site, in the lower end of the humerus, is more unusual. The metastases from renal-cell carcinoma are often a more expanding type of tumor than this — this tumor mass was only 2 5 by 5.0 cm. That is as far as I can go, since nothing is said in the record about examination of the prostate or kidneys.

I had the impression as I first read through the record that the most likely diagnosis would be an osteolytic form of osteogenic sarcoma. On looking at the x-ray films, however, a metastatic lesion seems more likely. In any lesion like this, we have been taught that the only approach is to consider it a malignant lesion of bone until proved otherwise, and that the only method by which an exact diagnosis can be made is by biopsy with preparation for amputation if the lesion proves to be malignant. If I have to make a definite diagnosis from the appearance of the x-ray film, I say that this was probably metastatic carcinoma, and that is as far as I am willing to go.

#### CLINICAL DIAGNOSIS

Sarcoma, (?) reticulum-cell type

#### DR. FRANSEEN'S DIAGNOSIS

Metastatic carcinoma

#### ANATOMICAL DIAGNOSIS

*Metastatic renal-cell carcinoma*

#### PATHOLOGICAL DISCUSSION

DR. EDWIN F. CAVE: I saw this man after he had been admitted to the Baker Memorial Hospital. He was wearing a splint on the right arm. He had a fracture through the diseased area of the lower end of the humerus, and a good deal of swelling of the distal end of the arm and elbow. We could not make an accurate diagnosis, so we did a biopsy, separating the muscles, which were edematous.

The radial nerve was retracted, and we came into the fracture line. The bone was spongy and rather necrotic, the medulla was easily entered, and we took specimens from the cortex, the medulla and the periosteum. An attempt was made to do frozen sections at the time, but nothing conclusive was determined from the sections, so we closed the wound and waited for a report.

DR. TRACY B. MALLORY: The tumor in this case was extensively necrotic, and not until the permanent sections were cut were we able to find areas suitable for diagnosis. When we finally got some viable tumor it was quite evident that we were dealing with carcinoma, with large, clear, vacuolated cells very strongly suggestive of renal origin. Will you go on from there, Dr. Cave?

DR. CAVE: We debated then whether we should study the patient further by doing an intravenous pyelogram. Dr. Grantley Taylor was asked to see him, and he agreed that amputation was indicated and we proceeded with that. Amputation was done about two weeks after the biopsy. We amputated through the surgical neck of the humerus. The wound healed primarily. After that Dr. Chute and Dr. Colby saw the patient, and renal studies were done.

DR. MALLORY: Dr. Wyman, will you show the pyelogram?

DR. WYMAN: The pyelogram shows a tumor in the upper portion of the kidney, displacing the calyces.

DR. RICHARD CHUTE: I was presented with this problem on account of the fact that a number of cases have been reported in which a solitary metastasis from a renal-cell carcinoma has been removed and later the original source found and removed, and the patient remained "cured" for a good number of years. It seemed to us reasonable to extirpate the focus, therefore, Dr. Soutter and I did a nephrectomy. Dr. Soutter might like to say something about the technic and the result.

DR. LAMAR SOUTTER: This is the third case of a transthoracic nephrectomy done in this hospital for carcinoma. The reason for using this approach is that it provides more room for radical surgery. The exposure is better to cut the renal vein on the right side of the spine and the renal artery at the aorta and to remove the regional lymph nodes and the adrenal gland. That was done in this case.

DR. MALLORY: The amputated arm showed a mass of necrotic tumor, again with recognizable areas of renal-cell adenocarcinoma, and the resected kidney showed characteristic hypernephroma. The tumor was extensive enough to have invaded the renal vein and extended along nearly two thirds of the way to the vena cava as they often do.

The patient is still convalescing on the wards and is doing well.



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## FEDERAL SUPPORT FOR MEDICAL EDUCATION

"THE philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow." Half a century ago Osler<sup>1</sup> thus indicated the fluctuations of thought with which men sometimes measure their problems and devise their solutions. The problems are always vivid and immediate, whereas their solutions seem limited — so limited that men find themselves able to move in only one direction or not at all. Wars become inevitable, and so do Government subsidies, but is this wisdom or is it foolishness? Medical education in the United States is today based upon the highest standards in the world and yet whenever it is surveyed it is easily shown to be inadequate and in immeasurable need

of improvement. In a less prodigal age we should have said that we were living far beyond our means, but none is living beyond his means today until he has completely exhausted all chance of Government support. The air is full of talk of such support for medical students, medical research, medical education and medical practice.

The American Academy of Pediatrics has recently released a recommendation for federal support of pediatric education.<sup>2</sup> The figures presented are said to reveal a startling lack of adequate training on the part of those who are caring for children. On the other hand if such figures were broken down into groups of those whose hospital training or lack thereof was received ten, twenty and thirty or more years ago, it might become apparent that we are on the very crest of a wave of improvement in pediatric training as judged by time spent in pediatric hospitals after graduation from medical school. Certainly there are more candidates than there are opportunities for approved residency training in pediatrics, and in all the other specialties as well. When one turns to the need for more physicians trained in the care of children in the remote and rural areas, fellowships are suggested for medical graduates "committed to return to practice in an area of need." Many have tried, but no good answer has yet been framed for the old question of how they are to be kept down on the farm. The cost of medical education to the student is also cited as a reason why there may be a tendency on the part of young doctors to renounce special training or to settle in the urban areas where professional life may be economically easier. The recommendations are specific that an appropriation of \$5,000,000 be authorized, to be administered by the Federal Security Administration in direct support of pediatric education. Half of this would go to the departments of pediatrics of the approved medical schools in accordance with need and student enrollment. One and a half million dollars is recommended for scholarships and fellowships or other purposes directly related to pediatric education, and \$1,000,000 is recommended for allocation to states in need because of their remote and rural areas into which physicians cannot now be induced to move.

Other specialties occupy educational grounds no less valid and deserving, what would be the tendency for them to generate equalizing pressures? Medical schools are constantly being surveyed by professional groups gathering data about this or that special interest. Such surveys are generally followed by reports indicating the existing inadequacies and suggesting minimum standards. It is as though our leaders were busying themselves by seeking to perfect each small part of a mosaic, but neglecting to concern themselves with the over-all picture or the condition likely to supervene ten years hence.

That the eyes of different groups are not focused upon the same objective is emphasized by recent divergent estimates concerning the likelihood of a shortage of physicians by 1960.<sup>3</sup> The United States Public Health Service and the Federal Security Administration anticipate a shortage of between 30,000 and 50,000 doctors in another decade, whereas the American Medical Association estimates that by 1960 there will be in this country at least 1 physician for every 700 people—a greater ratio than at present or in the immediate past. The number of physicians is increasing at a relatively more rapid rate than that of the population as a whole. This would be all right if there were to be more for them to do in the coming era than there has been in the past. If there are to be vast increases in hospital and research facilities more medical manpower will be needed. On the other hand, too many physicians, like too many cooks, could be a menace to the people's health, especially if it is necessary to sacrifice quality to produce the larger number, and if they must eke out a living by private practice in this apprehensive and neurotic world.

Whether an extension or permanent modification of the present GI bill of rights for all medical students would be helpful (and to whom) is another large subject. Such an extension would not produce more doctors. It might make medical education available to students who would otherwise seek a different training or vocation. It would surely attract the type of student whose hat is in the ring for a scholarship. Medicine has need for the best brains that can be recruited, it also needs character. Brains are more easily measured than character,

but character motivates and guides the application of brainpower, and is therefore recognized as a raw material without which a good doctor cannot be educated regardless of the resources at his disposal. If a formula could be devised that would recognize and attract character as readily as brains are now recognized, medical educators would find the task of selecting students greatly lightened and better performed than at present.

Expansion of federal largess is potentially without limit—but there is a fly in the lard. The members of the medical profession are not unanimously convinced that Government support can be contrived without Government interference. In a recent Washington Report<sup>4</sup> an aide of the Federal Security Administrator is quoted as asking the question

Why must Uncle Sam ever be suspected, when he lends a helping hand, of having something up his sleeve? Whoever can answer this question can also tell us whether all this is wisdom or foolishness.

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#### THE WORLD MEDICAL ORGANIZATION

POSSIBLY unnoted by many, in the present confused and disturbed condition of the world, was the announcement from the recent Interim Session of the House of Delegates of the American Medical Association in Cleveland on the formation of a World Medical Organization.

This was agreed to in principle at the Atlantic City Annual Session in June, 1947, and authority for participation wholeheartedly voted by the House of Delegates. The organization meeting was held in Paris in September, with four members of the Board of Trustees as the American representatives. One hundred and twenty-five delegates from forty-eight nations attended. From the reports on the sessions, one gathers that some of the meetings resembled those held by the United Nations at Lake Success. Apparently, there were many trying moments when patience, tolerance, long suffering

and vision were required" — not to be wondered at when one considers the diversity of tongues, suspicions and fears. Apparently, Drs Henderson, Bauer, Irons and Sensenich did a splendid piece of medical statesmanship. The details of the organization need not be reviewed here but should be read in the January 17 issue of the *Journal of the American Medical Association*, where they are briefly set forth.

A few essentials may be stated. This newly formed organization constitutes a potentially important agency for peace as well as health. It is to be distinguished from the World Health Organization, which is part of the United Nations set-up. It is to the medical picture what the American Medical Association is to American medicine, and the World Health Organization of the United Nations in that picture is comparable to the United States Public Health Service. Under the present temporary organization, illustrative of its broad international scope, the president is from Paris, the president-elect from Czechoslovakia, the treasurer from Switzerland, and the ten elected members of the General Council from England, Sweden, France, Spain, Australia, India, China, Cuba, Canada and the United States. The permanent secretariat is to be in New York City at the Academy of Medicine.

This organization may well prove to be the first step toward a better understanding among nations, and, if so, it will be of inestimable value. As has been well said, "If the doctors in the world cannot get together, it is doubtful if anyone can."

## DISPLACED PERSONS

MEMBERS of the medical profession are commonly accused of taking less interest in world affairs than the average responsible man with the same degree of education. It would be truer to say that specialized training has taught physicians the value of accurate detailed facts and the practical difficulty of obtaining them. Factual information about the 850,000 homeless people in Europe has recently been issued in a twenty-six-page pamphlet by the Citizens Committee on Displaced Persons with a view to clarifying the world problem that their plight has created.

These European ex-slave laborers have put the United States in a very embarrassing position indeed. It is *our* opposition to their forcible repatriation to Soviet-dominated countries and *our* insistence on their right to a home in a free country that is keeping them in concentration camps three years after the date of "liberation." To be sure, we are paying the bills. The camps in Germany and Austria are likely to cost us a quarter of a billion dollars in 1948. Not only our national economy but also our international reputation for good faith is being damaged. Fifty-three times in three months has the Soviet propaganda office broadcast the story to the world of how our great humanitarian democracy is letting its former allies rot in camps for displaced persons. France, Belgium and the United Kingdom have already admitted 6000, 20,000 and 24,000 displaced persons, respectively, as immigrants and have agreed to admit 69,000, 66,000 and 80,000 more in the immediate future. Other democracies have made similar commitments. The United States has admitted 22,000 and is now debating whether to admit any more.

It is not necessary to be vague regarding the type of persons represented. They have recently been investigated in their camps by a special nonpartisan committee of the House Foreign Affairs Committee and are being surveyed by a similar committee of the Senate. They are Poles, Latvians, Lithuanians, Estonians, Yugoslavs, Greeks, Ukrainians, Czechs and Jews — all homeless and all certain of persecution or death in their former countries. Half are women and children, almost all are young, and many are skilled. For example there are 21,175 skilled construction workers, including architects, draftsmen, surveyors, electricians and carpenters, 38,654 persons trained in the professions (teachers, musicians, librarians, nurses, physicians, artists, lawyers, engineers and so forth), 95,427 agricultural workers and many other representatives of valuable skills and trades listed in the most recent census. Investigators report them to be good citizenship material.

An emergency bill is before Congress (Stratton Bill, HR 2910) to admit approximately half the displaced persons to the United States by increasing the annual immigration quota for a period of four years. First priority would be given to the relatives

of United States citizens and veterans. If all who could qualify under our basic immigration laws were admitted they would amount to only 0.3 per cent of the population, or less than half the quota of immigrants whose admission to this country was prevented during the four war years. Secretary of State Marshall strongly favors this action and says, "Now is the time to act. Robert P. Patterson states that, 'on the grounds of economy, humanity and the furtherance of the world peace,' Congress should enact HR 2910. The presidents of the AFL and CIO believe that such action will not have any adverse bearing on the American workman' and that 'the DP's would in fact stimulate employment.'" Earl G. Harrison, former commissioner of immigration and now dean of the University of Pennsylvania Law School and chairman of the Citizens Committee on Displaced Persons has made the following comment:

Our rate of population growth has been slowing up and our population has been growing older. Immigration gave us strength and nonishment when we were young in the family of nations. It can help us again. It can give us the strong, vigorous population needed to maintain our leadership among world powers.

Justice Owen J. Roberts adds:

If we are serious in our concern for personal freedom we must prove it by action. If we make the gesture for DP's other countries will follow our lead.

The humanitarian aspect of this situation is easy enough to comprehend. The political, economic, financial and international phases are being clarified by the information now becoming available. A great many people whose opinions deserve unqualified respect believe that the Stratton Bill should be passed, and passed at once. We have become accustomed to suspect a joker in most election-year legislation, but it is difficult to find a joker in this bill.

## THE FALLACY OF THE CRUDE DEATH RATE

In a statement released by the Federal Security Administrator, Oscar R. Ewing, the crude death rates for the various states were discussed. In 1945 the death rate for the country as a whole was 10.6, whereas in 1946 it was 10.0. The reported rate for

Massachusetts dropped from 12.2 to 11.2, although there was an actual increase of 265 deaths. The only explanation for a decreased death rate with a practically constant number of deaths would be an increase in the population. Demobilization of troops caused an increase, but the extent is problematical, and at the present time estimated populations must be used in the determination of rates. Considerable error may also be found in such estimations when shifts in population have affected a large proportion of the people, such as occurred among civilians during the war years. Until the next census is taken, rates can only be approximated, and little significance should be placed in a reported drop in the crude death rate from 12.2 to 11.2.

The variations in the rates in different parts of the country are influenced by age, sex and race differences. An older part of the country, such as New England, is expected to have a higher death rate than that of the more recently settled communities. If valid comparisons of mortality risk are to be made, adjustments are necessary to allow for differences in population structure. It is interesting to note that, despite the many changes in the trends of individual disease as well as population changes, the total number of deaths in Massachusetts has remained fairly stationary for the last quarter century, averaging about 50,000 deaths per year.

## MASSACHUSETTS MEDICAL SOCIETY DEATHS

**BARTON** — John A. Barton, M.D., of Fitchburg died recently. He was in his sixty-seventh year. Dr. Barton received his degree from Harvard Medical School in 1897. He was head of the Eye, Ear, Nose and Throat Department of the Burbank Hospital for thirty years, and was a member of the New England Otolgical and Laryngological Society.

His widow, a son and a granddaughter survive.

**ELLIS** — Arthur H. Ellis, M.D., of Greenfield, died on March 4. He was in his sixty-seventh year.

Dr. Ellis received his degree from Dartmouth Medical School in 1907. He was a former president of Franklin District Medical Society and was a member of the staffs of Franklin County Public Hospital, Greenfield, and Farnen Memorial Hospital, Montague City, and a fellow of the American Medical Association.

His widow, four daughters and six grandchildren survive.

**EVERETT** — Frederick L. Everett, M.D., of Springfield died on March 6. He was in his seventy-sixth year. Dr. Everett received his degree from Cornell University Medical College in 1902.

His widow, two daughters and nine grandchildren survive.

**FISH** — John E. Fish, M.D., of Canton, died on March 30. He was in his seventy-fifth year.

Dr. Fish received his degree from Dartmouth Medical School in 1896. He was a former president of Norfolk District Medical Society and was formerly superintendent of the Massachusetts Hospital School in Canton. He was a fellow of the American Medical Association.

His widow, two daughters and two sons survive.

**HOSLEY** — Walter A. Hosley, M.D., of Topsfield, died on March 25. He was in his seventieth year.

Dr. Hosley received his degree from Harvard Medical School in 1904.

Two daughters survive.

**HUNT** — Reid Hunt, M.D., of Boston, died on March 7. He was in his seventy-eighth year.

Dr. Hunt received his degree from College of Physicians and Surgeons of Baltimore in 1896. He was associate professor of pharmacology at Johns Hopkins University School of Medicine from 1898 to 1903, chief of the division of pharmacology, United States Public Health Service, from 1904 to 1913 and professor of pharmacology at Harvard Medical School from 1913 to 1936. He was professor of pharmacology, emeritus, Harvard Medical School, a former chairman of the Council on Pharmacy and Chemistry of the American Medical Association and a member of the Association of American Physicians.

His widow survives.

**IRWIN** — Vincent J. Irwin, M.D., of Springfield, died on February 26. He was in his sixty-first year.

Dr. Irwin received his degree from Yale University School of Medicine in 1909. He was a member of the American Academy of Ophthalmology and Oto-Laryngology and a fellow of the American Medical Association.

His widow survives.

**LELAND** — Leslie P. Leland, M.D., of Worcester, died on March 16. He was in his sixty-fourth year.

Dr. Leland received his degree from Boston University School of Medicine in 1909. He was a former secretary of the Worcester District Medical Society and was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow and two daughters survive.

**MAY** — James V. May, M.D., of Belmont, died on December 24, 1947. He was in his seventy-fifth year.

Dr. May received his degree from University of Pennsylvania School of Medicine in 1897. He was a former president of the New England Society of Psychiatry, Massachusetts Psychiatric Society and American Psychiatric Association, and was a fellow of the American Medical Association.

**O'BRIEN** — John C. O'Brien, M.D., of Greenfield, died on March 18. He was in his eighty-fifth year.

Dr. O'Brien received his degree from University of Vermont College of Medicine in 1887. He was formerly a trustee of the Northampton State Hospital, town physician and physician to the Greenfield House of Correction, and was a fellow of the American Medical Association.

A son and a daughter survive.

## MEDICOLEGAL ABSTRACT

**Relation of Patient and Physician — Confidential communications and their possible disclosure in hospital records.** According to the terms of his oath the physician is bound to treat the communications of his patient in confidence. Legally, however, no such privilege existed under the common law. In some states, however, statutes have protected confidences revealed to the physician

for the purpose of adequate diagnosis and treatment. In states where such confidences are protected by statute the question may arise to what extent, if any, the protection is removed if the information revealed to the physician in confidence is made a part of a hospital record. Such a question was recently considered by the Supreme Court of Ohio.

In a proceeding in which it was sought to show that a will was invalid on the ground that the testator lacked the necessary mental capacity, hospital records were offered, consisting of the entrance slip, the physician's direction for the medication to be administered and treatment to be given the patient by the nurses, record of analyses of the blood and the urine of the patient and the day-to-day chart made and kept by the nurses who had charge of the patient while he was at the hospital. These charts recorded the food and medicine given and the condition and behavior of the patient, the fact that he was irrational at times, that he left his bed at unreasonable hours, that on one occasion he used a wastepaper basket as a commode, and that on several occasions he became unruly. Part of the record included notations of increasing administrations of sedatives culminating on the date that the will was signed. These portions of the record were all admitted in evidence. A verdict was returned that the writing in question was not valid as the last will and testament of the deceased, and judgment was entered for the contestant. The contestees sought a reversal on the grounds that the hospital record contained matters communicated confidentially to the physician and nurses of the deceased and should not have been admitted in evidence.

Ohio has statutes establishing a patient-physician privilege and also providing for the admissibility of hospital records, but the statutes do not specify the relation between the two. The court discussed the question whether or not the communications should have been admitted even though it found that the contestees had waived their privilege by permitting the physician to testify completely and without objection to all details of his diagnosis and treatment. However, the court stated:

The courts in most states having Physician-Patient Privilege Statutes similar to section 11494, General Code, generally hold that communications between Physician and Patient, not in the presence of third persons, for the purpose of diagnosis and treatment of the patient, if carried into a private hospital record or chart, remain confidential, and that such part of the chart or record is inadmissible in evidence unless the privilege is waived.

In discussing generally the admissibility of hospital records the court said:

Such a hospital or physician's office record may properly include case history, diagnosis by one qualified to make it, condition and treatment of the patient covering such items as temperature, pulse, respiration, symptoms, food and medicine given, analysis, of the tissues or fluids of the body, and the behavior of and complaints made by the patient.

The court drew a line between direct communication and observed facts or information obtained without communication. The difficulties in determining admissibility according to such a line of demarcation are evident. Portions of the record that report diagnosis and directions for treatment do not fall into either of the categories described by the court. Is the diagnosis admissible? And of what use is it to bar the communications on which diagnosis is based when the diagnosis and medication and directions for treatment clearly indicate the substance of the barred communication? In this case, therefore, part of the records included notations of increasing administration of sedatives that would be confidential if related to the physician by the patient but perhaps avoids the privilege when entered on the hospital record as an observed fact.

If the entire hospital record is admissible in evidence the purpose of the statute and of the physician's oath would be nullified, and professional confidence would be limited to unrecorded information (*Wes v Wes*, 72 N E [2nd] 245, 1947).

## MISCELLANY

### AMERICAN COLLEGE OF SURGEONS APPROVES USE OF NURSE ANESTHETISTS

The Board of Regents of the American College of Surgeons at a meeting on February 22, adopted the following resolution:

The American College of Surgeons regards with deep concern the actions of some physician anesthesiologists in giving the impression to the laity in the public press that it is unsafe for experienced nurse anesthetists to conduct surgical anesthesia. While it supports the increasing tendency of having physician anesthesiologists in charge of surgical anesthesia, it deplores at this time any propaganda for the elimination of the trained nurse anesthetist. On the contrary, the American College of Surgeons is of the opinion that, in view of the inadequacy in number of the physician anesthesiologists and in view of the splendid record of achievement of the nurse anesthetist institutions engaged in the training of nurses for this purpose should be encouraged to continue their programs.

### NATIONAL CANCER INSTITUTE

More than \$1 355,818 in federal grants in-aid from Public Health Service funds for cancer research and control has been announced by the Federal Security Administration. It was made on the recommendation of the National Advisory Cancer Council of the National Cancer Institute. Another \$8 000 000 in construction grants for new laboratory and clinical facilities has been recommended by the Council.

## NOTE

Dr Arthur Marvel Lassek, head of the Department of Anatomy, Medical College of the State of South Carolina in Charleston since 1935 has been appointed Waterhouse Professor of Anatomy at Boston University School of Medicine, effective July 1. Dr Lassek will succeed Dr Jesse LeRoy Conel, a member of the medical faculty since 1923.

## CORRESPONDENCE

### RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held March 18 it was voted to restore the registration to practice medicine to Dr George J. Orlandi, 20 Charlotte Road Newton Centre (formerly of 1234 Blue Hill Avenue Dorchester).

H QUINBY GALLUPE, M.D. Secretary

State House  
Boston

## DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held March 18 it was voted to suspend the registration of Dr William P. Pratt 28 Adams Street, Quincy, for three months.

H QUINBY GALLUPE, M.D. Secretary

State House  
Boston

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*An Atlas of Anatomy*. By J. C. Boileau Grant, M.C., M.B. (Ch.B. F.R.C.S. (Edin.)) professor of anatomy in the University of Toronto. Second edition. 4 cloth 496 pp., with 991 illustrations. Baltimore: Williams and Wilkins Company, 1947. \$10.00.

This atlas was published first in 1943 and reprinted in 1944 and 1945. Dr Grant, in this edition has added more than two hundred illustrations including the wrist, superficial veins of the limbs, the inguinal region, abdominal viscera, suprathyroid region, mouth and the blood supply of the esophagus, stomach, duodenum, pancreas, bile passages, spleen and suprarenal glands. Also, the more common dissecting room variations, the epiphyses and schemes of the distribution of the cranial nerves and of the motor nerves to the extremities are considered. A good index concludes the volume. The book is well published in every way. The illustrations and color work are excellent. The atlas is recommended for all medical libraries.

*Overcoming Stammering*. By Charles Pellman. With a foreword by Frederick Martin, M.D., director of National Institute for Voice Disorders, Bristol, Rhode Island, and director of Speech Clinics, State Department of Education, Rhode Island. 8 cloth 160 pp. New York: The Beechurst Press, 1947. \$3.00.

Mr Pellman, an experienced practicing speech correctionist, analyzes and evaluates current methods of speech correction and treatment. He presents a plan for speech correction of stammering and stuttering based upon the physiology of speech and proper mental hygiene rather than on the functioning of the speech apparatus. His method may be used in the home by intelligent parents. The text ends with an autobiographic sketch of a stammerer by Aaron Pellman. A list of books and an index conclude the volume. The book is well published. It is recommended for medical and educational libraries.

*Procedure in Examination of the Lungs, with Especial Reference to the Diagnosis of Tuberculosis*. By Arthur F. Kraetzer, M.D., associate attending physician, Lenox Hill Hospital, physician to outpatients, New York Hospital and Instructor in medicine (dermatology), Cornell University Medical College. Third edition revised and with a preface by Jacob Segal, M.D. medical director, Los Angeles Sanatorium. Oxford Medical Publications. 8° cloth, 150 pp. with 16 illustrations and 14 plates. New York: Oxford University Press, 1947. \$3.50.

Dr Segal, in this revision of Kraetzer's manual has brought the subject up to date since the publication of the previous edition in 1935. The text of the second edition has not been disturbed, but the new material has been incorporated in an appendix of twenty-two pages and sixteen x-ray plates. An x-ray commentary on the correlation of signs leading to a diagnosis with histories of 13 cases and illustrated with the x-ray pictures, is included in the appendix. An index has been added for the first time. The volume is well printed with good type on good paper.

*The Dispensatory of the United States of America* By Arthur Osol, Ph G, M S, Ph D, professor of chemistry and director of the department of chemistry, Philadelphia College of Pharmacy and Science, and George E Farrar, Jr, M D, associate professor of medicine, School of Medicine, Temple University, and chief of Medical Service A, Episcopal Hospital 4<sup>th</sup>, cloth, 1928 pp Philadelphia J B Lippincott Company, 1947 \$16 50

This standard reference work has a remarkable record of one hundred and fifteen years of continuous publication. It was first issued in 1833 as *The Dispensatory of the United States of America*, by Drs George B Wood and Franklin Bache. In 1879, with the fourteenth edition, Dr H C Wood became associated with the elder Dr Wood, and in 1885, with the fifteenth edition, Dr H C Wood became the principal author. With the centennial edition Dr H C Wood, Jr, became the principal author, and he is now advisory editor to this twenty-fourth edition. The work was issued every few years from the beginning, and a number of editions were reprinted, except that editions were not published during the Civil War years, 1859-1864. The text is divided into five parts. Parts one and two, the major portion of the work, describe the drugs recognized by the *United States Pharmacopæia*, the *Pharmacopæia of Great Britain* or the *National Formulary* and the drugs not official in these works. The drugs are listed alphabetically in these two sections. The remaining parts list general tests, processes, reagents and solutions, veterinary uses and doses of drugs, and tables of the *United States Pharmacopæia* or the *National Formulary*. The tables on atomic and molecular weights, and on equivalents of weights and measures are especially valuable. A comprehensive index concludes the volume. The publishing is excellent in every way. Every effort has been made to reduce the weight and size of such a large volume. The text is printed in two columns on a good light paper with a good type. The price is very reasonable for the size of the book. The work is recommended for all libraries, medical and general, and to all persons interested in drugs.

*The Foot and Ankle Their injuries, diseases, deformities and disabilities* By Philip Lewin, M D, associate professor of bone and joint surgery, and acting head of department, Northwestern University School of Medicine, professor of orthopedic surgery, Post-Graduate Medical School of Cook County Hospital, attending orthopedic surgeon, Cook County Hospital, senior attending orthopedic surgeon, Michael Reese Hospital, and consulting orthopedic surgeon, Municipal Contagious Disease Hospital, Chicago. Third edition 8<sup>th</sup>, cloth, 847 pp, with 389 illustrations. With line drawings by Harold Laufman, M D. Philadelphia Lea and Febiger, 1947 \$11 00

This edition of a standard work has been extensively revised in the light of the vast amount of information gleaned from the records and experience of World War II. Much material has been added, and emphasis has been placed on compound fractures, crushing wounds and osteomyelitis. There is a special chapter on the military aspects of foot and ankle disorders. The sections on traumatic gangrene and amputations have been enlarged, and ringworm has been considered not only as a primary and sole infection but also as a complication of injuries. There is a special chapter on psychosomatic medicine as it relates to certain orthopedic conditions. The book is well published and is recommended for all medical libraries and to all persons interested in the subject.

*Diseases of the Nose, Throat and Ear* By William L Ballenger, M D, and Howard C Ballenger, M D, associate professor and acting chairman, Department of Otolaryngology, Northwestern University School of Medicine, Chicago, and surgeon, Department of Otolaryngology, Evanston Hospital, Evanston, Illinois. Assisted by John J Ballenger, M D, research fellow in otolaryngology, Northwestern University School of Medicine, Chicago. Ninth edition 8<sup>th</sup>, cloth, 993 pp, with 597 illustrations. Philadelphia Lea and Febiger, 1947 \$12 50

This edition of an authoritative textbook has been revised by the addition of much material. Obsolete material has been deleted, and portions of the text rewritten and amplified. There is a new chapter on "headaches and neuralgias of the face," and rhinoplastic reconstruction has been described. The special contributors have revised the chapters on arytenoidectomy for bilateral paralysis of the recurrent laryngeal nerves,

physiology and functional tests of the labyrinth and inflammatory diseases of the labyrinth and peroral endoscopy. The volume is well published in every way. The printing of a history of the editions on the back of the title page would be of value to reviewers and other interested persons. The book is recommended for all medical reference collections.

*Textbook of General Surgery* By Warren H Cole, M D, professor of surgery and head, Department of Surgery, University of Illinois College of Medicine, and director of surgical service, Illinois Research and Educational Hospitals, Chicago, and Robert Elman, M D, professor of clinical surgery, Washington University School of Medicine, assistant surgeon, Barnes Hospital, associate surgeon, St. Louis Children's Hospital, and director of surgical service, H G Phillips Hospital, St. Louis. Fifth edition 8<sup>th</sup>, cloth, 1160 pp, with 558 illustrations. New York D Appleton-Century Company, 1948 \$11 00

This standard textbook, first published in 1939 and last revised in 1944, in this new edition has been thoroughly revised to date. The type has been completely reset, and the volume repaged. The chapters on war and catastrophe surgery, surgical diseases of the chest and chemotherapy have been rewritten. The chapter on the nutritional requirements of surgical patients has been considerably expanded. A chapter has been added on surgical convalescence, including preoperative and postoperative care. The text is well written, and the material well organized. Selected references are appended to each chapter. Indexes of authors and subjects conclude the volume. The publishing is excellent except that the coated paper makes the volume heavy for its size. It is recommended for all medical libraries and all surgeons.

*A Text-Book of Bacteriology* By R W Fairbrother, M D, D Sc (Man), F R C P (Lond), director of the department of clinical pathology, Manchester Royal Infirmary, and special lecturer in bacteriology, University of Manchester. Fifth edition 8<sup>th</sup>, cloth, 480 pp, with 34 tables and 6 plates. New York Grunc and Stratton, 1948 \$6 50

This textbook, first published in 1937, and last revised in 1946, has gone through twelve printings of the five editions, a fact that attests its soundness as a textbook for students. The author has made a thorough revision of the text for this fifth edition. The book is an outline of the medical aspects of bacteriology. The material is divided into three parts: general bacteriology, systematic bacteriology and general technique. A good index concludes the volume, which is well printed with a good type by the lithographic process on light paper.

*Blood Pressure and Its Disorders, including Angina Pectoris* By John Plesch, M D, Budapest, M D, Germany, L R C P and S Edin and Glas. Second edition revised and enlarged 8<sup>th</sup>, cloth, 307 pp, with 125 illustrations. Baltimore Williams and Wilkins Company, 1947 \$6 00

Dr Plesch has revised this second edition of his monograph, first published in 1944, by the addition of material, chapters and case histories. Selected references have been appended to each chapter. The text represents the author's personal experience and research, and is not intended as a comprehensive treatise on the subject. The printing was done in Great Britain and is excellent. The type and paper are good. The book should prove useful to physicians interested in the subject.

*Biochemistry for Medical Students* By William V Thorpe, M A (Cantab), Ph D (Lond), reader in chemical physiology, University of Birmingham. Fourth edition 8<sup>th</sup>, cloth, 496 pp, with 36 illustrations. Baltimore Williams and Wilkins Company, 1947 \$5 00

This English textbook, first published in 1938, and last revised in 1943, has been revised to date. A chapter on the use of isotopes in biochemical investigations has been added, and the sections on protein structure, coenzymes, flavo-proteins, bile pigments and nutrition in wartime have been largely rewritten. The text is well written, and the material well organized. The type, printing and paper are excellent. The book should prove useful as an excellent summary of the subject.

*Malaria, with Special Reference to the African Forms* By W. K. Blackie M.D., Ph.D. F.R.C.P. (Edin.), D.T.M. & H. 8<sup>th</sup> cloth 104 pp., with a color plate Cape Town The African Bookman for the Post-Graduate Press 1947 10sh., 6d

This concise monograph presents the latest methods of treatment with quinine and the newest plasmodicidal drugs including mepacrine (atabrine), pamaquin and paludrine. The first chapter comprises a short historical review followed by chapters on the parasitology, pathology, clinical features, diagnosis, prognosis, treatment and prophylaxis of the various types of the disease. The material is well organized and well published in every way. The color plate depicting the various plasmodiae is excellent. A good index concludes the text. The monograph was published by the Bayer Pharma. publication fund of the Cape Town Post-Graduate Medical Association. The work is recommended for all medical libraries.

*Nursing in Modern Society* By Mary Ella Chayer, R.N. M.A. associate professor of nursing education Teachers College Columbia University 8<sup>th</sup> cloth 288 pp New York G. P. Putnam's Sons 1947 34.00.

This book has been written primarily for nurses, teachers and supervisors. The various current problems of nursing are discussed by the author in the following divisions: the impact of social forces upon nursing, the influence of social forces upon community health needs and building a better future for the nursing profession. Miss Chayer has called attention to the changing needs of society and to the changes that have already taken place in the nursing profession. The last chapter summarizes the twelve cardinal principles of professional service. The text is well written in an easy style, and the material is well organized. The type paper and printing are excellent. A list of references and one of questions for study are appended to each chapter. A comprehensive general bibliography and a good index conclude the volume. The work should prove useful as a reference work in schools of nursing and as a textbook for postgraduate students. It is recommended for the reference collections of all medical libraries.

*Benjamin Silliman 1779-1864 Pathfinder in American Science* By John F. Fulton, M.D. and Elizabeth H. Thomson 8<sup>th</sup> cloth, 294 pp. with seventeen illustrations New York Henry Schuman 1947 \$4.00

Benjamin Silliman is of interest to the medical historian because of the responsible part he took in organizing Yale University School of Medicine in 1813. He was eminent as a chemist and geologist and as a teacher of science. He established the great Peabody Museum of natural history and founded the first gallery of fine arts in an American academic institution, the Trumbull Gallery of Yale College. He was also largely instrumental in founding the Sheffield Scientific School, first called the School of Applied Chemistry. The authors of this well written biography for the general reader cover the professional life of Silliman from the time he was appointed professor of chemistry at Yale in 1802 until his retirement in 1853. The story is told in an easy narrative style. The book is well published and should be in all medical and scientific historical collections. It is one of a series in *The Life of Science Library*.

*400 Years of a Doctor's Life* Collected and arranged by George Rosen M.D., and Beate Caspar-Rosen, M.D. 8<sup>th</sup> cloth 429 pp New York Henry Schuman 1947 \$5.00.

This interesting anthology is made up of excerpts taken from formal autobiographies, letters and other writings of physicians, dead and living of the past four hundred years. The material is arranged according to epochs and incidents in a doctor's life: early years, school days, medical student days, the practice of medicine, scientist, scholar and teacher, the doctor marries, the doctor as a patient, the doctor goes to war, writing and politics; and reflections on life and death. The selections are preceded by short biographic notes or comments. The absence of direct references to the sources of the selections will be decry by the historian and bibliographer. A number of physicians appear more than once in different sections of the text and there should have

been an index to names to make the book useful as a reference work. The type, printing and paper are excellent. This unusual historical book should be in all collections of medical and general history.

*Calcium and Phosphorus in Foods and Nutrition* By Henry C. Sherman Ph.D. Mitchell Professor of Chemistry emeritus Columbia University 8<sup>th</sup> cloth 176 pp with seven figures and twelve tables New York Columbia University Press 1947 \$2.75

This semipopular monograph presents in plain language a summary of the place of calcium and phosphorus in present-day nutrition. The first chapter discusses the role of calcium and phosphorus in nature, in agriculture and in human nutrition. The following chapters deal with calcium in the body, the effects of food and growth upon the calcium content, chemical forms and nutritional functions of phosphorus, calcium and phosphorus requirements and the problem of necessary and optimal intakes and foods as a factor in the nutritional provision of calcium and phosphorus. An extensive bibliography of forty-four pages is appended to the text. A good index concludes the volume. The text is well written in a pleasing style and the material is well organized. The publishing is excellent. The printing is well done with a good type on a good light paper. The volume is recommended for all medical and general libraries and to all persons interested in the subject.

*Surgical Disorders of the Chest: Diagnosis and treatment* By J. K. Donaldson M.D. associate professor of surgery and in charge of thoracic surgery University of Arkansas School of Medicine, and member of surgical staff, St. Vincent's Infirmary and visiting staff, Baptist Hospital, Little Rock, Arkansas. Second edition thoroughly revised 8<sup>th</sup> cloth 485 pp with 146 illustrations and 2 color plates Philadelphia Lea and Febiger 1947 \$8.50.

This new edition of a standard treatise has been revised to include the knowledge gained during World War II. Decortication of the lung is discussed in some detail. Selected references are appended to each chapter and a good index concludes the volume. The publishing is excellent in every way. The book is recommended for all medical libraries and to surgeons interested in the subject.

*Principles of Occupational Therapy* Edited by Helen S. Willard A.B. O.T.R. director Philadelphia School of Occupational Therapy and Clare S. Spackman, S.M. in Ed. O.T.R. director, curative workshop Philadelphia School of Occupational Therapy director Occupational Therapy Department Hospital of the Graduate School of Medicine University of Pennsylvania and assistant director, Philadelphia School of Occupational Therapy 8<sup>th</sup> cloth 416 pp with 46 illustrations Philadelphia J. B. Lippincott Company 1947 \$4.50.

This new textbook is the joint work of twenty specialists in the field of occupational therapy. The text is divided into two sections, basic concepts and applied principles. The first section deals with the history, development, scope, educational aims and activities of the subject and factors in the organization of occupational therapy departments. The second section discusses the place of the therapy in general and special hospitals with a chapter on children's hospitals and pediatric services and in United States Army and Navy hospitals during World War II. In this section there are chapters on the use of occupational therapy for patients with mental disease and tuberculosis, the visually handicapped and for patients with physical injuries. The last chapter of over a hundred pages is subdivided into three sections dealing with treatment for limitation of motion of joints, flaccid paralysis and Industrial Injuries, for patients afflicted with cerebral palsy and for arthritic patients. The treatment is given in detail. The concluding chapter describes the rehabilitation program of the Veterans Administration. The work constitutes a treatise on the philosophy and practice of the subject. The text is well written, and the organization of the material is good. The volume is well published. The type is good and legible, and the printing on a soft, light paper pleasing to the eye is excellent. The book should be in all medical libraries and should prove valuable to all persons interested in physical therapy.



*A Text-Book of Mental Deficiency (Amentia)* By A F Tredgold, M D, F R C P, F R S (Ed), consulting physician to University College Hospital, London Seventh edition 8°, cloth, 534 pp., with 47 plates and 9 tables Baltimore Williams and Wilkins Company, 1947 \$8 50

This new edition of a standard textbook, last revised in 1937, has been brought up to date by the addition of considerable material. Some chapters have been rewritten, and the changes made by the British Education Act of 1944 relating to educationally subnormal and defective children have been incorporated in the chapter on English law concerning mental defectives. A good index concludes the volume. The text, printed in Great Britain, is well done with a good type on good paper. The book is recommended for all medical libraries and to all persons interested in the subject.

## NOTICES

### ANNOUNCEMENT

Dr Franklin G Balch, Jr, announces the removal of his office to 1180 Beacon Street, Brookline, for the practice of general surgery.

### SUFFOLK DISTRICT MEDICAL SOCIETY

The Suffolk District Medical Society will meet in Sprague Hall, Boston Medical Library, 8 Fenway, Boston, on Tuesday, May 4. The councilors will meet at 3 30 p m, and the annual meeting will be held at 5 00 p m.

### MASSACHUSETTS SOCIETY FOR SOCIAL HYGIENE

The annual meeting of the Massachusetts Society for Social Hygiene will be held at a dinner at the Boston City Club, 14 Somerset Street, Boston, on Wednesday, April 28, 6 00 p m. *Guest speaker* Dr Raymond A Vonderlehr of Atlanta, Georgia, medical director, Communicable Disease Center, United States Public Health Service, will speak on the subject "Past, Present and Future Responsibilities of the Social Hygiene Societies in the Control of the Venereal Diseases." Dr William A Hinton, chief of the Wassermann Laboratory, State Department of Public Health, and chief of the Laboratory Division of the Boston Dispensary, will be another guest of honor at the dinner. Dr George Gilbert Smith will preside.

The public is cordially invited to attend. For details regarding the program, reservations for the dinner and so forth, application should be made in writing or by telephone to the office of the Massachusetts Society for Social Hygiene, 1145 Little Building, Hancock 6-3176.

### NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the auditorium, Boston University School of Medicine, 80 East Concord Street, Boston, on Monday, April 26, at 8 15 p m. Dr James M Faulkner will preside.

#### PROGRAM

Diphtheritic Myocarditis Drs Norman H Boyer and Louis Weinstein

Clinical and Laboratory Features of First Attacks of Rheumatic Fever Occurring in Scarlet-Fever Patients Treated with Penicillin Drs Louis Weinstein, Louis Bachrach and Norman H Boyer

Acceleration of Flow in the Veins of Human Limbs by the Local Application of Pressure Drs Joseph R Stanton, Edward D Freis and Robert W Wilkins

Some Observations Concerning the Effect of Sympathectomy on the Human Heart Rate Drs Reginald H Smithwick, Earle M Chapman, Dera Kinsey and George P Whitelaw

The Effects of Veratrum Viride in Hypertensive Man Drs Edward D Freis, Joseph R Stanton, James W Culbertson, Julius Litter and Meyer H Halperin

Interested physicians and medical students are cordially invited to attend.

### NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular meeting of the New England Society of Physical Medicine will be held at the Ring Sanatorium and Hospital, Arlington, Massachusetts, on Wednesday, April 21, at 8 p m. Dr Volta R Hall will speak on the topic "Physical Medicine in the Treatment of Psychiatric Conditions."

Members of the medical profession are cordially invited.

### AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION

The annual meeting of the American Clinical and Climatological Association will be held at White Sulphur Springs, West Virginia, from November 1 to 3 (secretary, James Bordley, III, M D, Mary Imogene Bassett Hospital, Cooperstown, New York).

### AMERICAN CONGRESS OF PHYSICAL MEDICINE

The twenty-sixth annual scientific and clinical session of the American Congress of Physical Medicine will be held from September 7 to 11, inclusive, at the Hotel Statler, Washington, D C. Scientific and clinical sessions open to members of the medical profession in good standing with the American Medical Association will be given.

Full information may be obtained by application to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois.

### AMERICAN NEUROLOGICAL ASSOCIATION

The annual meeting of the American Neurological Association will be held in Atlantic City, New Jersey, from June 14 to 16, with headquarters at the Claridge Hotel (secretary-treasurer, H Houston Merritt, M D, Montefiore Hospital, Gun Hill Road, New York 67, New York).

### AMERICAN SOCIETY OF ANESTHESIOLOGISTS INC

A joint meeting of the American Society of Anesthesiologists, Inc, and the Western Divisions of the Canadian Anaesthetists' Society will be held at the Hotel Saskatchewan, Regina, Saskatchewan, Canada, on April 23 and 24. Physicians and medical students are invited.

### MAINE MEDICAL ASSOCIATION

The annual meeting of the Maine Medical Association will be held in Poland Spring from June 20 to 22 (secretary, Frederick R Carter, M D, 142 High Street, Portland 3, Maine).

### MINNESOTA STATE MEDICAL ASSOCIATION

The annual meeting of the Minnesota State Medical Association will be held in Minneapolis from June 7 to 9 (secretary, B B Souster, M D, Lowry Medical Arts Building, St Paul 2, Minnesota).

### MONTANA STATE MEDICAL ASSOCIATION

The annual meeting of the Montana State Medical Association will be held in Billings on June 18 and 19 (secretary, H T Caraway, M D, 115 North 28th Street, Billings, Montana).

### NEW MEXICO MEDICAL SOCIETY

The annual meeting of the New Mexico Medical Society will be held in Las Vegas from June 3 to 5 (secretary, H L January, M D, 221 West Central Avenue, Albuquerque, New Mexico).

(Notices concluded on page viii)

## NOTICES (Continued from page 582)

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY APRIL 22

## FRIDAY APRIL 23

- \*9:00-10:00 a.m. Relief of Pain by Neurosurgical Procedures. Dr. William H. Sweet, Joseph H. Pratt Diagnostic Hospital.  
 \*10:00 a.m.-11:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

## MONDAY APRIL 26

- \*12:00 p.m. Clinicopathological Conference Margaret Jewett Hall Mt. Auburn Hospital Cambridge  
 \*8:15 p.m. New England Heart Association Auditorium, Boston University School of Medicine

## TUESDAY APRIL 27

- \*12:15-1:15 p.m. Clinicopathological Conference Peter Bent Brigham Hospital  
 \*1:30-2:30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital

## WEDNESDAY APRIL 28

- \*9:00-10:00 a.m. Newer Concepts of Muscle Contraction Dr. Gerhard Schmidt, Joseph H. Pratt Diagnostic Hospital  
 \*12:00 p.m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
 \*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater Children's Hospital  
 \*6:00 p.m. Massachusetts Society for Social Hygiene. Boston City Club

\*Open to the medical profession

- APRIL 19-23. American College of Physicians. Page xlii, issue of July 31  
 APRIL 20. Greater Boston Medical Society. Page 543 issue of April 8  
 APRIL 20. South End Medical Club. Page 543 issue of April 8  
 APRIL 21. New England Society of Physical Medicine. Page 582  
 APRIL 21 and 24. American Society of Anesthesiologists, Inc. Page 582.  
 APRIL 26. New England Heart Association. Page 582  
 APRIL 26-29. American Dermatological Association. Page 456, issue of March 25  
 APRIL 28. Massachusetts Society for Social Hygiene. Page 582  
 APRIL 29-MAY 2. American Academy of Pediatrics. Page 240 issue of February 12.  
 MAY 30 and MAY 31. American Gastro-Enterological Association. Page 456, issue of March 25  
 MAY 1. Suffolk District Medical Society. Page 543 issue of April 8  
 MAY 3. American Society for Clinical Investigation. Page 456, issue of March 25  
 MAY 3 and 4. Association of American Physicians. Page 492, issue of April 1  
 MAY 4. Suffolk District Medical Society. Annual Meeting. Page 582  
 MAY 4 and 5. Association of Military Surgeons of the United States. Page 456, issue of March 25  
 MAY 6. Suffolk Censors Meeting. Page 344 issue of March 4  
 MAY 6-8. American Association for the Study of Goiter. Page xlii issue of July 31  
 MAY 9-14. American Psychiatric Association. Page 492, issue of April 1  
 MAY 11. Harvard Medical Society. Amphitheater of Building D Harvard Medical School. 8:00 p.m.  
 MAY 12-14. American Association of Genito-Urinary Surgeons. Skypot Lodge, Skypot Pennsylvania.  
 MAY 12. Indications for the Use of Forceps. Dr. Roy J. Hoffman, Perinatal Association of Physicians. 8:30 p.m. Haverhill  
 MAY 16-23. American Board of Obstetrics and Gynecology Inc. Page 344, issue of March 4.  
 MAY 16-23. International College of Surgeons. Page 136, issue of January 22.  
 MAY 17-19. American Ophthalmological Society. Page 492, issue of April 1.  
 MAY 17-20. American Urological Association. Hotel Statler Boston.  
 MAY 17-20. Association for the Study of Internal Secretions. Page 492 issue of April 1  
 MAY 18-22. American Association on Mental Deficiency. Copley Plaza Hotel, Boston  
 MAY 20-25. American Board of Ophthalmology. Page 170, issue of January 29  
 MAY 21-28. American Physiotherapy Association. Page 543 issue of April 8.  
 MAY 24-26. American Gynecological Society. Page 543 issue of April 8.  
 MAY 25-27. Massachusetts Medical Society. Annual Meeting. Hotel Statler Boston.  
 MAY 27-29. American Surgical Association. Page 455 issue of March 25  
 JUNE 7-10. National Gastroenterological Association. Page 455 issue of March 25  
 JUNE 14-16. American Neurological Association. Page 582.  
 JUNE 17-20. American College of Chest Physicians. Page 455 issue of March 25  
 JUNE 20 and 21. American Radium Society. Page 543 issue of April 8.  
 JUNE 21 and 22. American Society for the Study of Sterility. Page 384, issue of March 11

- JUNE 25 and 26. Christian Medical Society. Page 492 issue of April 1  
 JUNE 28-30. American Academy of Pediatrics. Hotel Schroeder Milwaukee Wisconsin  
 JULY 6-74. Students International Clinical Congress. Page 455 issue of March 25  
 JULY 12-17. First International Polymyositis Conference. Page 36, issue of January 1  
 AUGUST 11-21. International Congress on Mental Health. Page 344 issue of March 4  
 AUGUST 23-4. International Society of Hematology. Page 417 issue of March 18  
 AUGUST 26-28. American Association of Blood Banks. Page 420 issue of March 18  
 SEPTEMBER 7-11. American Congress of Physical Medicine. Page 582  
 SEPTEMBER 13-15. American Academy of Pediatrics. Olympic Hotel Seattle Washington  
 SEPTEMBER 20-23. American Hospital Association. Page 310 issue of February 26.  
 SEPTEMBER 29. Mississippi Valley Medical Editors Association. Page 170 issue of January 29  
 OCTOBER 6-9. American Board of Ophthalmology. Page 170 issue of January 29  
 NOVEMBER 1-3. American Clinical and Climatological Association. Page 582  
 NOVEMBER 8-12. American Public Health Association. Page 420 issue of March 18  
 NOVEMBER 20-23. American Academy of Pediatrics. Annual Meeting. Chalfont-Haddon Hall Hotel Atlantic City New Jersey  
 DECEMBER 7-9. Southern Surgical Association. Annual Meeting. P. 543 issue of April 8.

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

- MAY 11. Annual Meeting. Hotel Weldon, Greenfield

## MIDDLESEX EAST

- MAY 12. Annual Meeting. 6:45 p.m. Bear Hill Golf Club Wakefield

## PLYMOUTH

- MAY 20. Lakeville Sanatorium, Lakeville.

## SUFFOLK

- MAY 1. Spring Dinner  
 MAY 4. Annual Meeting  
 MAY 6. Censors Meeting

## WORCESTER

- MAY 12. Annual Meeting

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## CARCINOMA OF THE STOMACH\*

CLAUDE E. WELCH, M.D.,† AND ARTHUR W. ALLEN, M.D.‡

BOSTON

**S**URGICAL experience with carcinoma of the stomach at the Massachusetts General Hospital has been reviewed by Parsons<sup>1</sup> in previous papers covering the years 1922 to 1926, and the period from 1927 to 1936 by Parsons and Welch.<sup>2</sup> This report includes all patients admitted to this hospital on whom the diagnosis was made during the ten-year period 1937 to 1946 inclusive.

In the compilation of these figures, it is, of course, our hope to show that increased knowledge of the disease and its amenability to surgical attack have resulted in a steadily increasing five-year salvage rate. But it is of equal importance to consider the trends in management of patients with cancer of the stomach. In this brief summary, only our own experience can be considered, and no attempt is made to cover the voluminous literature comprehensively.

Several methods can be listed by means of which the curability rate can be increased. They are as follows: earlier diagnosis, that more patients with carcinoma will arrive in the hospital in a curable stage, more radical approach to the problem of gastric ulcer, that a certain number of cancers masquerading as ulcers will not be overlooked, extension of the type of operation so that by a wider excision of involved tissue, more cures may be obtained, and a reduction in the postoperative mortality, so that cases favorable for cure are not lost.

### DELAY BEFORE TREATMENT

Theoretically, if all patients were subjected to resection as soon as carcinoma of the stomach developed, all would be cured. Early diagnosis is therefore of the utmost importance. A vivid illustration of this point is furnished by the following case.

F. C. (M.G.H. 61931), a 58-year-old man entered the hospital on June 27, 1934, because he had vomited blood three times in the previous month. X-ray studies including

an upper gastrointestinal series, were negative. Gastroscopy showed chronic gastritis. Because of the possibility of carcinoma of the stomach, exploratory operation was performed. A 2-cm lymph node, found on the greater curvature, on frozen section showed 'highly malignant carcinoma. Because metastasis was already present, the surgeon did only a local excision of a small carcinoma of the greater curvature and did not remove any other lymph nodes. The pathological report was adenocarcinoma. The patient was living and well 12 years later. Despite the high malignancy of the tumor and an inadequate operation, early surgery effected a cure.

Cancer of the stomach, once established, is usually a very rapidly growing tumor. This is shown by the rarity of cancers of the stomach discovered incidentally at post-mortem examination, when death is due to some other cause. This behavior is in contrast to that of carcinoma of the prostate, which is not uncommonly discovered in autopsy specimens as an incidental finding.

This behavior of carcinoma of the stomach has been recognized for many decades, and a vast amount of educational information has been spread by various cancer-control groups in an effort to bring the patient with gastric symptoms to the surgeon in time for cure. At the same time, the medical profession has become more alert to the problem, and early diagnosis has been facilitated by better x-ray films and an increased use of the gastroscope.

It seemed probable, therefore, that a comparison of the delay before treatment would show a significant decrease in this last decade. To obtain comparable series, the length of time that elapsed from the onset of gastric symptoms to the date that the patient entered the hospital for treatment was determined for all patients undergoing operation during the twenty-year period 1927 to 1946. The delay in the first ten-year period was then contrasted with that in the latter (Fig. 1). The remarkable and unhappy result is that the two curves can be almost exactly superimposed.

Why does the average delay before treatment still remain at the high level of five months? Is it apathy on the part of the patient or neglect by the physician? One is inclined to believe that all

\*Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 3, 1947.

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educational efforts have been negated by the radio and advertising columns with their promises of "relief for acid indigestion." Perhaps the medical profession should be satisfied that it is not fighting a losing battle against this propaganda, and conclude that if the public wishes to be cured of cancer of the stomach, it had better do something to aid itself.

No special attempt has been made in this study to discover the length of life of the untreated cases. It has been shown by Nathanson and Welch<sup>3</sup> and by Livingston and Pack<sup>4</sup> that the average duration

of life is about a year from onset of symptoms, and that 90 per cent of all patients are dead at the end of two years. The average delay from onset of symptoms to hospital entry of patients not subjected to surgery in the present series was about six months, at that time, operation was judged unwise or was refused by the patient.

Once the patient has been admitted to the hospital, he is studied completely. Endoscopy, as Benedict<sup>5</sup> has shown, is of great value, especially with lesions high in the stomach, since esophageal involvement may be observed. Peritoneoscopy is often valuable, especially if the patient has no symptoms of obstruction. If hepatic or peritoneal metastases are found, in the absence of obstruction, an operative procedure is contraindicated. On the other hand, if obstruction is present, the exploration is nearly always recommended, even if metastases are present, in the hope that a short-circuit may make the patient's life more comfortable.

TABLE 1 Types of Therapy Employed in All Cases of Carcinoma of the Stomach

PERIOD	TOTAL NO OF CASES	NO OF OPERATION	LAPAROTOMY ONLY	PALLIATIVE OPERATION	RESECTION
1927-1931	296	115	55	58	68
1932-1936	395	135	88	69	103
1937-1941	375	95	73	36	171
1942-1946	457	105	85	22	245

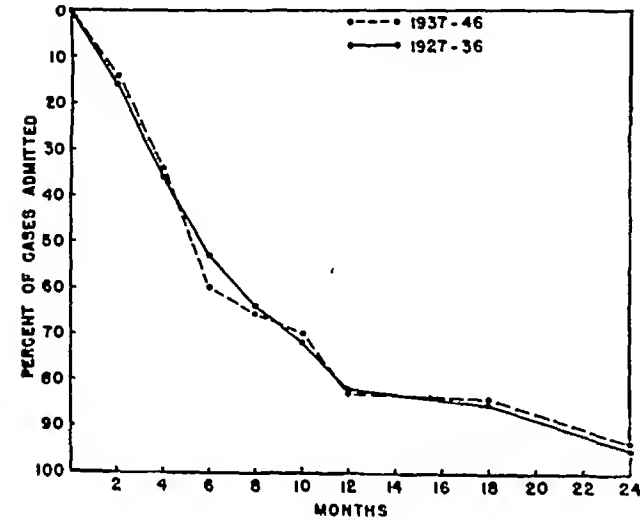


FIGURE 1 Delay in Seeking Treatment among All Cases of Cancer of the Stomach in Which Operation Was Performed. The duration of symptoms before hospital admission is divided into ten-year periods.

The therapeutic procedures employed in the various periods are listed in Table 1.

THE PROBLEM OF GASTRIC ULCER

The well known fact that gastric cancer frequently simulates benign gastric ulcer needs re-emphasis.

able, if healing is complete, repeat observation should be made one month after discharge from the hospital.

Another method of determining the diagnosis is by means of the cytologic smear, according to Papanicolaou's<sup>7</sup> technic. Fresh gastric washings are precipitated and stained. If malignant cells are found, the diagnosis is almost surely carcinoma. On the other hand, with known cancer of the stomach, the smear will be positive in only about two thirds of the cases. Thus, in the Vincent Memorial laboratory, the results to date have been as follows: in 50 cases of gastric ulcer or cancer in which gastric smears were employed, 24 patients proved to have carcinoma of the stomach, and the smears were positive in 15, of 26 patients without cancer, the smear was reported positive in 1, who proved to have a benign ulcer.<sup>8</sup>

If these recommendations are followed, there will be no significant delay in the recognition of gastric cancers. Furthermore, the very rare case of cancer that will "heal" under the best medical therapy (we have had at least 2 cases in this hospital) will soon be discovered, for the ulceration will recur after the patient leaves the hospital.

That the differential diagnosis of ulcer and cancer is still difficult is attested by the fact that 11 per cent of all the resections in the patients in the present study were made with the preoperative diagnosis of benign gastric ulcer. Fortunately, the delay before operation has been diminished in this group, because it has become appreciated that gastric resection for gastric ulcer produces excellent results, as shown by St. John et al.<sup>9</sup> and Judd and Priestley.<sup>10</sup>

One may ask how many lives might be saved if all the gastric carcinomas in this group were recognized and surgery performed at an early date. Since about 25 patients with apparent gastric ulcer appear in a year in this hospital, of whom about 14 per cent have carcinomas, 3 or 4 patients will be subjected to an earlier resection. Since the five-year curability rate is at least 40 per cent in this group, at least one additional cure a year should be expected in this hospital by early resection. But it is imperative for the surgeon to realize that, even when he has the stomach in his hands, he cannot make the differential diagnosis between ulcer and cancer, and that he must carry out the proper operation for gastric cancer.

#### EXTENSION OF THE OPERATIVE PROCEDURE

Gastric resection for carcinoma originally involved no attempt to excise any tissue but that of the stomach itself. However, the importance of removal of the regional lymph nodes along the lesser and greater curvatures was soon recognized, since the earliest metastases are usually found there. A second feature was emphasized by Castleman,<sup>11</sup> who showed the frequency of invasion of the proximal centimeter of duodenum by cancer of the stomach; he found that extension rarely proceeded beyond this level. A third site of early extension pointed out by Ogilvie<sup>12</sup> and Allen<sup>13</sup> is the great omentum. Metastases there are not uncommon, and may be overlooked except on microscopical section.

These three areas — the regional lymph nodes, the proximal centimeter of duodenum and the great omentum — should be removed with every resection for cancer of the stomach in which cure is the objective. Of course, if disease is to be left behind in other spots inaccessible to surgical removal, and only a palliative resection is planned, there is no need to remove the omentum in every case, although it is usually better to do so. After a long experience with this procedure, we are convinced that it carries no hazard and may contribute to a smoother convalescence.

As a corollary to the concept that gastric ulcer should be considered to be cancer until the pathologist proves it to be benign, it follows that the same operation should be carried out for gastric ulcer as for gastric cancer — that is, the removal of regional lymph nodes, great omentum and proximal duodenum. There is nothing more distressing to the surgeon than to read the pathologist's report

"carcinoma of the stomach, no lymph nodes are included with the specimen." Yet this happens all too frequently, and many patients who should have the best chances of cure are doomed because of an inadequate operation.

Proximal extension of carcinoma of the stomach to the cardia often requires the procedure of total gastrectomy. This operation, although mentioned in the previous report, was a surgical rarity at that time. The technic as subsequently developed and described by Allen<sup>13</sup> has been followed in this hospital. Since the patients subjected to the procedure usually have extensive tumors, the mortality rate is bound to be high, and the number of cures small. The postoperative life span, however, is often surprisingly long.

The operation of total gastrectomy, in addition to an increased postoperative mortality, has other undesirable features. After operation, it is difficult for many patients to maintain adequate nutrition, and an anemia of significant grade is not uncommon. Studies of patients who have had recurrence after subtotal resections for cancer usually show that metastatic involvement of lymph nodes is present but that the remaining stomach is uninvolved. For these reasons, we do not subscribe to Longmire's<sup>14</sup> theory that all patients with carcinoma of the stomach should be treated by total gastrectomy.

The operative attack on carcinoma of the stomach, has, in the past, been limited by inaccessible proximal extension of the growth into the esophagus and mediastinum. Although it was frequently possible to draw down 3 to 5 cm. of the esophagus and do a total abdominal gastrectomy, in many cases it was impossible to get an adequate margin above the tumor. Recently, Churchill<sup>15</sup> and Sweet,<sup>16</sup> in pioneer work in this hospital, have developed the technic of transthoracic gastrectomy. With this approach through the diaphragm, extension of the cancer into the esophagus is easily amenable to resection.

There are several organs that can be sacrificed, resection en bloc with the carcinoma of the stomach being used. Thus, the transverse colon, the pancreas, the spleen and rarely a local extension into the liver can be resected with the tumor. It is our experience that none of these patients will survive five years, but recurrence of the disease will be delayed.

There are, unfortunately, many areas of metastasis that cannot be removed surgically. Metastatic lymph nodes in the head of the pancreas about the superior mesenteric artery or about the hepatic artery are nearly always nonresectable. Whereas a regional lymph-node dissection of the left gastric artery may be done, a cure is not to be expected if the nodes about the celiac axis are involved. Metastatic lesions in the liver, if demonstrable, are indicative of widespread involvement of the organ. Removal of visible hepatic metastases will not

tribute to the postoperative comfort of the patient or increase the five-year survival rate. Peritoneal metastases are likewise indicative of widespread lymphatic involvement, local removal is useless.

The question might be asked regarding the relative importance of these extensions of the operative procedure so far as the control of cancer of the stomach is concerned. Five-year survivals are not to be expected if other viscera are involved as well as the stomach, so that massive resections of multiple viscera should be considered of value only as palliative procedures. On the other hand, there are rare

continued parenterally several days afterward. Sodium sulfadiazine was employed intravenously for some time before penicillin was available, and is still utilized in some cases. The sulfonamides cannot be used locally with safety, and, as a rule, they may be employed for only a short time because of the danger of renal complications.

Blood replacement has also played an important role. It is essential to remember that a normal red-cell count and hematocrit may be misleading in any given patient, since the blood volume may be low, as Lyons<sup>18</sup> has pointed out. Blood is now given

TABLE 2 Mortality with Various Types of Gastric Resection

TYPE OF OPERATION	NO. OF CASES		OPERATIVE DEATHS		OPERATIVE MORTALITY	
	1937-1941	1942-1946	1937-1941	1942-1946	1937-1941 %	1942-1946 %
Abdominal approach						
Subtotal palliative resection	35	32	13	2	37	6
Subtotal resection for cure	96	99	11	3	11	3
Total resection	35	34	17	11	49	32
Transthoracic approach						
Subtotal resection	4	48	2	2	50	4
Total resection	1	32	1	9	100	28
Totals	171	245	44	27		
Averages					26	11

five-year survivals after total gastrectomy. Obviously, the transthoracic approach has opened a new field that cannot yet be appraised accurately.

REDUCTION OF POSTOPERATIVE MORTALITY

The method of increasing the number of five-year cures of cancer of the stomach that has heretofore seemed to offer the most promise has been the reduction of excessive postoperative mortality. Thus, in the period 1932 to 1936, the mortality of gastric resection for cancer was 25 per cent. If these patients had not died, the five-year cures following resection would have increased by the same percentage.

It is gratifying to note that the mortality of resections has declined appreciably in recent years. The factors that have contributed are chiefly improved anesthesia, more careful blood, protein and vitamin replacement and chemotherapy. The anesthetic agent now employed is most commonly ether, by intratracheal administration, although our choice in patients who are not to have the diaphragm opened is continuous novocain administered in the spinal area by the method of Arrowood and Foldes.<sup>17</sup>

Local and parenteral use of penicillin just before, during and after operation has contributed a great deal to a smooth convalescence. Especially in transthoracic approaches, Sweet<sup>18</sup> has found that the use of penicillin has practically eliminated the complication of empyema. It appears to be no less effective in the peritoneal cavity. For full effect, it should be started before operation and

very liberally, therefore, despite normal laboratory figures. Likewise, intravenous amigen or amino acids and vitamins are administered in large doses when indicated preoperatively and as a routine measure postoperatively.

A technical contribution of great importance is that of Allen and Donaldson,<sup>19</sup> who introduced the routine use of double jejunostomy after gastric resections. The proximal tube is led back through the gastroenterostomy, and the distal one serves as a jejunostomy for feeding. Thus, the stomach is decompressed postoperatively without the use of a Levine tube. Stomal obstruction, which occurred in about 1 out of 20 patients in the series of Allen and Welch,<sup>20</sup> is no longer to be feared as a complication.

Although pulmonary emboli have not been eliminated as a cause of death, they have been reduced in number in recent years by prophylactic ligation of the superficial femoral veins, by the method of Allen, Linton and Donaldson.<sup>21</sup> We believe that this procedure is indicated in any patient who has a curable lesion, preferably at the time of resection, or within forty-eight hours thereafter.

These advances in therapy have resulted in a definite decrease in the number of postoperative deaths. Table 2 and Figure 2 show that the percentage of postoperative deaths has consistently diminished although the operability has increased.

To determine the effect of postoperative mortality on the curability rate, it is necessary to divide the resections into various groups (Table 2). Subtotal resections "for cure" represent cases in which the

surgeon has removed all gross cancer from the abdomen, and is the group that actually contains nearly all the cured patients "Palliative" subtotal resections include cases in which cancer is left behind in inaccessible areas at the time of resection, no cures are to be expected. With total gastrectomies five-year cures are very rare, whereas trans-thoracic gastrectomies have not been done long enough to evaluate the curability rate. Hence, only subtotal resections for cure need be considered

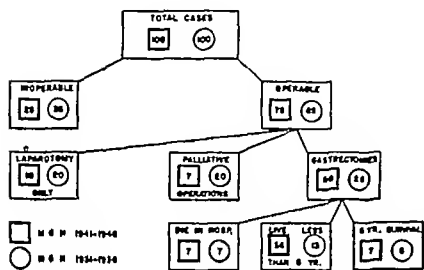


FIGURE 2. Prognosis in Cancer of the Stomach. The fate of all patients entering the hospital with this diagnosis is demonstrated by decades.

The postoperative mortality in this group was 11 per cent in 1937 to 1941 and 3 per cent from 1942 to 1946. This means that the factor of postoperative mortality can, at present, no longer be reduced significantly, and that other methods must be found to increase the number of cures.

#### FIVE-YEAR SURVIVALS

What, then, is the ultimate fate of the patient who enters the hospital with carcinoma of the stomach? A graphic summary, comparing the results of the present decade with those of the last, is given in Figure 2, in which the results from 1927 to 1936 are shown by the circled figures. The results in the present series are included in the heavy squares. Incidentally, it may be noted that, in the last five-year series in which it was possible to determine end-result so far as five-year cures are concerned (1937 to 1941), only 4 patients have been untraced. They are considered in the tables to be dead of disease. Several trends are immediately discernible: the number of apparently operable patients has risen from 65 per cent to a level of 75 per cent, the patients who have an operation are much more likely to have a gastrectomy than they were before (50 per cent of all cases, compared with 25 per cent), whereas the percentages of exploratory laparotomies remain about the same and those of palliative operations other than gastrectomy have decreased, in the cases of gastrectomy, there is

little change in the number of hospital deaths, and many more patients live up to four years after operation, and the over-all number of five-year cures has increased from about 5 per cent to 7 per cent.

It is clear that the great increase in the number of gastrectomies is due to the more widespread use of resection as the best palliative operation, even if all gross disease cannot be removed. The increased number of palliative resections has maintained the over-all mortality for resection at the same level as that of the previous study.

A further analysis of the gastrectomies performed is presented in Figure 3. There were no five-year survivals in the patients who had gross disease left in the abdomen, and only a rare five-year survival after total gastrectomy. Practically all the favorable cases fell into the group of subtotal resections, in which all gross cancer is removed.

The statement has sometimes been made that, even if gross cancer is left behind in the abdomen, a cure may result. Our information lends no credence to that claim. Eighty-five per cent of the patients with palliative subtotal gastrectomy were dead a year after operation, and all were dead two years after operation. The average postoperative length of life was about eight months.

Since the average length of life after exploratory laparotomy alone for cancer of the stomach is about six months, palliative gastric resections cannot be defended on the basis that a significant pro-

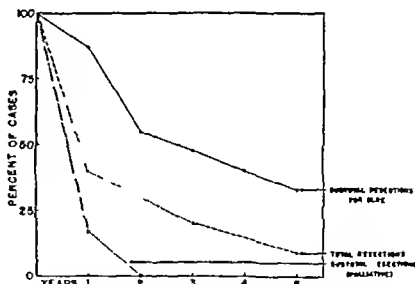


FIGURE 3. Duration of Life after Various Types of Gastric Resections for Cancer (1937-1941).

longation of life results. On the other hand, patients who have had an obstructing lesion removed are usually more comfortable and may die a relatively painless death from hepatic or pulmonary metastases. Since some patients without hope of cure are condemned to life for a period after operation, such a resection is really palliative. It seems justifiable to continue the use of the term "palliative gastrectomy" to distinguish operations in which gross disease is left behind in the abdomen.



Livingston and Pack<sup>4</sup> have used the term "resectable cancer of the stomach" to describe cases in which all gross cancer can be excised. This is a valuable term, and in the present study is represented by all the subtotal resections, total resections and those done by the transthoracic route in which all gross disease can be removed. In the present series, the mortality for "resectable cancer" is 19 per cent, and the five-year curability is 20 per cent.

The prognosis of any case of carcinoma of the stomach may be gauged fairly accurately by microscopic examination of the specimen. The presence of metastasis to the regional lymph nodes is very

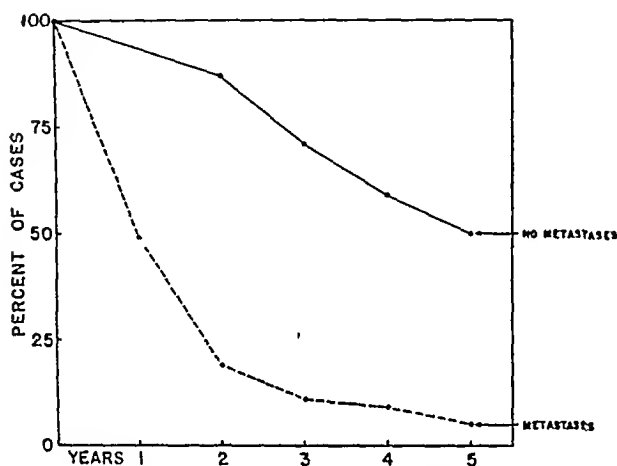


FIGURE 4 *Metastasis and Postoperative Duration of Life after Gastric Resection for Cancer*

*The end-results of all survivals indicate the importance of metastases in the determination of prognosis*

grave. Thus, in the years 1937 to 1941, there were 73 operative survivors who had metastases. Only 4 patients, or 5 per cent, lived five years. On the other hand, of the 42 patients who survived operation and had no extension to the regional nodes 20, or about 50 per cent, lived five years (Fig 4).

#### DISCUSSION

Livingston and Pack,<sup>4</sup> in their very complete survey of the treatment and end-results of gastric cancer, present many figures that are interesting to compare with this present series. It must be pointed out that their monograph was published in 1939 and that all clinics have improved their results since then. Thus, Pack<sup>22</sup> has recently reported that the operability in the Memorial Hospital has risen to 50 per cent. Therefore, no special credit need be taken by the Massachusetts General Hospital, except to point out that, here as well as elsewhere, modest gains have been registered in the therapy of cancer of the stomach.

Livingston and Pack state that there is no report in the literature in which the resectability was over 36.4 per cent and that the average rate was 18.7 per cent. Marshall and Welch,<sup>23</sup> in a recent report from the Lahey Clinic, found that 24.1 per cent of all patients with a diagnosis of cancer of the stomach in the years 1936 to 1940 had a resection. Somewhat similar figures were reported by Counseller<sup>24</sup> from the Mayo Clinic, where resection is carried out in 30 per cent of the patients with a diagnosis of gastric cancer. In our series, 50 per cent had resections, in 16 per cent inaccessible gross disease was left behind, whereas in 34 per cent all gross cancer was excised. The high resectability in this group has contributed to a comparatively high over-all postoperative mortality — 22 per cent. However, during the last five years of the study, although the resectability has increased from 45 to 54 per cent, the postoperative mortality has been reduced to 11 per cent.

Livingston and Pack also found that the average rate of postoperative five-year survivals from surgical treatment in the clinics studied was less than 2 per cent of the patients observed, the best rate reported from any surgical clinic or cancer center has never exceeded 5.2 per cent. In this series, from the years 1937 to 1941 (the last period available for end-results), there were 7 per cent five-year survivals.\*

#### SUMMARY

A study of all the patients with carcinoma of the stomach admitted to the Massachusetts General Hospital during the ten-year period 1937 to 1946 shows that the delay before treatment has remained unchanged, averaging five months. A more aggressive attitude toward gastric ulcer has increased the recognition of early cancer of the stomach.

The introduction of a transthoracic approach and the wider use of total abdominal gastrectomy have increased the number of cases available for resection.

The mortality for gastric resections for cancer has dropped to a present level of 17 per cent for the entire series and to 11 per cent in the last five-year period. The mortality of subtotal resections in which all gross disease is removed has been 3 per cent in the last five-year period.

Meanwhile, the number of unoperated patients has declined so that 75 per cent have an operation. Fifty per cent of the total have a gastrectomy, either subtotal or total.

The best palliative operation, if gross disease cannot be removed, is subtotal gastrectomy.

The five-year survival rate is now 7 per cent of the entire group that enters the hospital.

The most fruitful method now available to increase the number of cures of cancer of the stomach

\*Since this article was submitted for publication, State, Moore and Wangenstein<sup>25</sup> have surveyed the patients with carcinoma of the stomach entering the University of Minnesota Hospital from 1936 to 1945. Their figures show a 55.2 per cent resectability, with a mortality of 16.6 per cent, and an over-all five-year salvage of 6.6 per cent.

is to reduce the delay from onset of symptoms to surgical intervention

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## COMPLETE HEART BLOCK\*

### A Study of Two Cases in Veterans of World War II

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A NUMBER of reports in the medical literature emphasize the fact that some patients with complete heart block may have a favorable prognosis regarding life and the ability to perform daily tasks. In nearly every case the conduction defect is thought to be congenital in origin. Campbell,<sup>1</sup> in his discussion of congenital complete heart block, states that, "if there are no complications carrying special risks of their own, the prognosis is good and will probably prove that the condition is compatible with survival to old age." The cases reported below emphasize the ability of people affected with this malady to lead normal lives and at times to undergo rather strenuous exertion without demonstrable ill effects. Both patients were veterans of World War II. Only 1 case is reported in the literature in which a patient with complete heart block, apparently congenital in origin, was a member of the armed forces.<sup>1</sup>

## CASE REPORTS

**CASE 1.** A 34 year-old man reported to the Out Patient Department on June 11, 1947, for compensation examination because of complete heart block. He had been inducted into the service on December 7, 1943. Preinduction physical examination had revealed a resting pulse rate of 54

rising to 80 on exercise. The remaining examination revealed no abnormalities. After induction he completed 8 weeks of basic training. During a routine screening examination, a systolic apical murmur was heard, and the patient

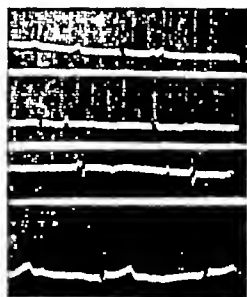


FIGURE 1. Tracing Obtained in Case 1 on May 15, 1943. Showing Complete Atrioventricular Dissociation with an Atrial Rate between 53 and 60 and a Ventricular Rate of 43. The T waves are upright in Lead I, biphasic in Lead 2, and inverted in Lead 3. The T waves in Lead 4 are upright.

was hospitalized for observation. An electrocardiogram taken on May 15 had shown complete heart block with a biphasic T wave in Lead I, inverted T waves in Leads 2 and 3 and an upright T wave in Lead 4 (Fig. 1). No other

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significant abnormality had been demonstrated during the study. The patient had been discharged from the service on June 5 and had subsequently been employed as a night clerk in a hotel, where he performed general manual labor.

The past history revealed a normal birth after a normal period of gestation. As a child the patient had measles, mumps, chicken pox and pertussis. At the age of 23, while playing baseball, he suddenly fainted. Since that time he had experienced six similar episodes, the last occurring at the age of 28 years. Additional medical history revealed that when the patient was 25 years old he had been told that he had a "bad heart." There was no history of scarlet fever, rheumatic fever, tuberculosis, syphilis or diabetes. The patient had attended school until he was 13 years old. At that time he completed the sixth grade, he incurred no difficulty in learning, but his schooling was stopped owing to the death of his father, whose position as a bread winner the patient accepted. At first he worked as a farm hand and later as a

Fluoroscopic examination of the heart showed the cardiac silhouette to be normal in size and shape.

An electrocardiogram revealed a complete heart block, with a diphasic T wave in Lead I and inverted T waves in Leads 2, 3 and F<sub>4</sub> (Fig 2).

**CASE 2** A 19-year-old veteran reported to the Out-Patient Department for treatment because of "heart trouble" and "weakness."

The patient had been a premature baby and had supposedly weighed only 3 pounds at birth. A further developmental history did not reveal anything unusual. The patient had had measles, mumps, whooping cough and chicken pox. After the period of childhood, except for occasional sore throat, he had never been sick. There was no history of scarlet fever, rheumatic fever, tuberculosis, diphtheria or syphilis. He gave a history of two syncopal attacks, both occurring at the pre-school age. No details concerning these episodes

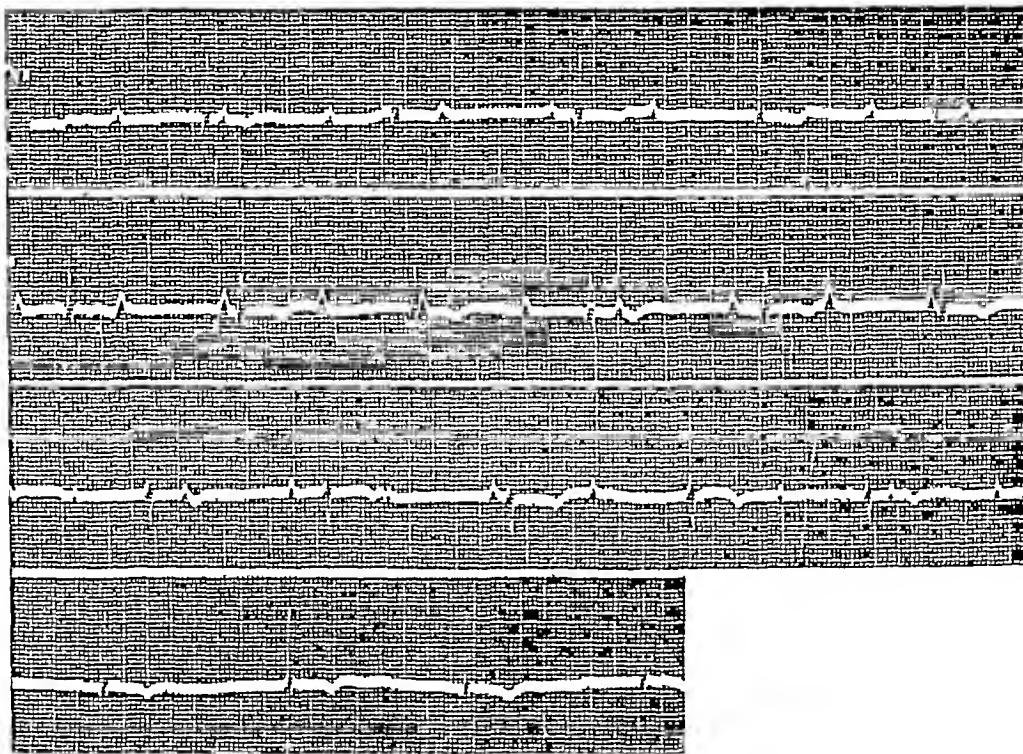


FIGURE 2 Electrocardiogram Obtained in Case 1 on June 11, 1947, Showing Complete Heart Block. Note the T-wave changes that have taken place since the last observation.

laborer on a railroad. He also held a job in a canning factory and finally was employed as a guard in a defense plant. He had no difficulty performing any of these tasks.

The family history was irrelevant.

Physical examination revealed a well developed and well nourished man who appeared to be in excellent health. The height was 69 inches, and the weight 175 pounds. An exercise-tolerance test, consisting of stepping on and off a chair 18 inches high twenty-five times, caused only a mild dyspnea. Examination of the heart showed no enlargement. There was a Grade I, blowing, systolic apical murmur transmitted only slightly toward the sternum. The murmur was somewhat accentuated by exercise. The remainder of the physical examination disclosed nothing of note.

The blood pressure was 120/80. The resting pulse was 52, rising to 80 after exercise.

Examination of the blood disclosed a red-cell count of 4,450,000 and a white-cell count of 6000, with 66 per cent neutrophils and 34 per cent lymphocytes. The sedimentation rate was 1 mm in 1 hour.

were obtainable. While in school he had no difficulty keeping up with other children. He was a member of the high-school basketball team. After completing 2 years of high school education, he went to work for a packing company. This called for arduous manual labor, which he was able to perform without any ill effects. His next job was that of a truck driver. He subsequently passed a physical examination for a Civil Service position, which he held until his enlistment in the United States Navy on January 5, 1945. Physical examination performed prior to enlistment showed a pulse rate of 48, which increased to 56 with exercise. The remainder of the examination was reported as showing nothing of note. The patient was accepted for duty with the Navy and had no difficulty until April 25, 1945, when he reported to sick bay because of an upper respiratory infection. At the time of admission to the hospital the pulse rate was 44, "increasing only slightly with exercise." A diagnosis of complete heart block was made, the diagnosis being confirmed by a number of electrocardiographic tracings. The patient was discharged from the service on July 10 and subsequently re-

turned to his old job, that of a truck driver. He was unable to perform his duties as well as he did before he entered the Navy because, as he put it, 'he felt weak all over'.

The family history was of no consequence.

Physical examination disclosed a patient of hyposthenic habitus. He did not appear either acutely or chronically ill. An exercise tolerance test consisting of stepping on and off a chair 18 inches high revealed only a mild dyspnea. Examination of the heart disclosed some enlargement to the left, the left border of cardiac dullness being slightly outside the midclavicular line. No thrills were palpable either

rate as compared with acquired complete heart block. The study of the 2 subjects revealed some evidence that may justifiably be construed as indicative of disease of the heart other than the conduction defect. In Case 1 there was an associated progressive inversion of the T waves in Leads 1, 2, 3 and F<sub>4</sub>. This may have been due to some obscure pathologic process, possibly infectious in origin, in-



FIGURE 3. *Electrocardiogram in Case 2 Showing Complete Heart Block, with an Atrial Rate of Approximately 60 and a Ventricular Rate of 33.3. No other significant abnormalities are noted.*

before or after exercise. There was a Grade II blowing aortic murmur, which was best heard in the third and fourth interspaces just to the left of the sternum. This murmur was transmitted toward the apex and was somewhat accentuated by exercise. The remainder of the examination was negative.

The pulse rate was 40, regularly increasing to 52 with exercise. The blood pressure was 140/70.

Fluoroscopic examination showed a mild enlargement of both the right and left ventricles.

An electrocardiogram revealed a complete heart block (Fig. 3).

#### DISCUSSION

It is true that the etiology of the heart block in the cases reported above is open to question. However, the following findings strongly suggested the congenital origin of the conduction defect: the absence of an acquired etiologic agent that is known to affect the myocardium, the ability of the patients to lead normal lives and at times to undergo rather strenuous exertion without demonstrable ill effects, and the presence of a relatively faster pulse

rate as compared with the myocardium or the pericardium, or both, or to a process involving the coronary arteries. No definite conclusion can be reached at present. In Case 2 the systolic murmur coupled with the enlargement of the heart might perhaps be ascribed to the increased stroke volume associated with the slow heart rate.

A review of the literature regarding congenital complete heart block showed a lack of uniform criteria to which a case must conform before it may be assumed to be congenital in origin. Yater,<sup>3</sup> in a review of this subject in 1929, pointed out certain requirements that should be fulfilled before a diagnosis of congenital complete heart block can be made. These are as follows: electrocardiographic proof of heart block, a record of a slow pulse at an early age, and absence of a history of infection, especially diphtheria, rheumatic fever, chorea or congenital syphilis. He also stated that syncope

attacks at a fairly early age and the presence of other congenital heart lesions add weight to the congenital etiology of the heart block. Most writers assume that complete heart block in children and young adults is to be considered infectious in origin until proved otherwise. Recently, different ideas were expressed.<sup>1,3</sup> Leys<sup>4</sup> points out that permanent complete heart block following infection is rare and also states that the burden of proof lies on the shoulders of the one who assumes that a case of complete heart block in young adults is due to infection. White<sup>5</sup> asserts that permanent heart block following an acute infectious process is rare and that the most frequent cause of complete heart block is coronary-artery disease. Campbell,<sup>6</sup> in a review of 64 cases of complete heart block, found that 13 per cent were congenital in origin, and slightly over 10 per cent could be accounted for by syphilis and rheumatic fever. Seventy-five per cent of the cases were due to coronary-artery disease.

Subjective complaints caused by congenital complete heart block are few. A small percentage of the patients experience Stokes-Adams attacks or shortness of breath, or both, on moderate exertion. Others develop neurasthenia after learning about their malady.

Yater<sup>2</sup> calls attention to the relative infrequency of cyanosis in these patients. When cyanosis is found, it is probably due to an accompanying heart lesion rather than to the heart block per se. Physical examination usually reveals a pulse rate of 40 to 50 and an enlarged heart. This cardiac enlargement may be attributed to an associated heart lesion or to prolonged diastolic filling due to slow heart rate.

It is of great practical importance to differentiate congenital complete heart block from the acquired condition, for the prognosis for life and the capacity to lead normal lives is good in congenital heart block. In a series of 8 cases that Campbell<sup>1</sup> followed for nine years he reported 2 deaths. The average sur-

vival rate for the other 6 patients was twenty-two years on last examination. The ages of these patients ranged from twenty-two to forty-two years. Jaleski and Morrison<sup>7</sup> reported a case in a thirty-one-year-old woman with congenital complete heart block who went through two terms of pregnancy and delivery without any complications. Levine<sup>8</sup> mentions a fifty-five-year-old patient who was known to have had complete heart block since the age of six, probably of congenital origin. The optimistic outlook in congenital complete heart block mentioned above should be contrasted with life expectancy in acquired heart block. The studies of Campbell<sup>6</sup> and Graybiel and White<sup>9</sup> show that approximately 70 per cent of patients with acquired heart block died less than three years after the discovery of the lesion. The remaining 30 per cent were alive after an average of six to seven years.

### SUMMARY

Two cases of complete heart block, probably congenital in origin, in veterans of World War II are presented.

The significant clinical aspects of congenital complete heart block are discussed.

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## VACCINATION AGAINST INFLUENZA A AND B\*

## A Comparison of Reactions, Doses and Titer Responses of Two Different Vaccines in Infants and Children

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ALTHOUGH numerous investigators have reported success in protecting adults from influenza A and B, very few studies are available in infants and children. A quantitative evaluation of the titer responses in this age group to various doses and types of vaccines was undertaken, as well as a study of the local and systemic reactions

## METHOD

The inoculations of vaccine were given subcutaneously from 9 to 10 a m. Temperatures were taken at four-hour intervals, and changes were computed by comparison with the patient's previous temperature record. The maximum rise was

TABLE 1 Temperature Elevations

VACCINE	DOSE cc	MEAN OF MAXIMUM ELEVATIONS F	RANGE OF MAXIMUM ELEVATIONS F	SUBJECTS WITH SLIGHT ELEVATIONS*		SUBJECTS WITH MODERATE ELEVATIONS†		SUBJECTS WITH MARKED ELEVATIONS‡	
				NO.	PER CENTAGE	NO.	PER CENTAGE	NO.	PER CENTAGE
1	0.5	1.19	-0.2 to +4.6	25	51	17	36	5	11
2	0.5	0.48	-0.4 to +1.6	34	79	9	21	0	0
1	1.0	1.12	-0.2 to +4.0	6	60	15	10	5	10
2	1.0	0.57	-0.4 to +4.0	35	76	10	22	1	2

\*Less than 1 F

†1.0 to 2.9 F

‡3 F or higher

to the vaccines. Adams, Thigpen and Rickard<sup>1</sup> showed that the immune response to influenza A infection was equally great in young infants and older children.

A group of 245 children, ranging in age from one to sixteen years and interned in one building for residua of poliomyelitis, were the subjects of this study. The children were divided into five groups, all of which were nearly comparable in age distribution. The first two groups received 0.5-cc and 1-cc doses of vaccine 1 ¶. The second two groups received the same doses of vaccine 2 ||. The fifth group was not vaccinated, but early and later serum titer studies were done as in the first four groups. This study was carried out in November and December, 1946.

determined in each of 186 cases, as well as the mean maximum for each group.

The local reaction was evaluated immediately, and at intervals of approximately twenty-four hours for thirty days.

Samples of blood were obtained before the vaccine was given and fourteen days after its administration. The viruses used in the quantitative titer determinations were those of influenza A (PR 8 strain) and influenza B (Lee strain). The photoelectric densitometer was employed after the method described by Hirst and Pickels.<sup>2</sup> All the four hundred and fifty-six determinations were done in pairs and in large lots.

## RESULTS

## Temperature

The means of the maximum temperature elevations are presented in Table 1. The values show that 0.5 cc of a vaccine gave the same average temperature rise as 1 cc of the same vaccine. Vaccine 1 caused a significantly higher temperature response than vaccine 2. Many children receiving the former had temperatures well over 100°F. The maximum temperature elevation occurred most frequently eight to twelve hours after vaccination.

## Local Reaction

The infection of vaccine 1 caused a sharp, stinging  
 \*  
 †  
 ‡

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†Aided by grants from the Graduate School of the University of Minnesota and The National Foundation for Infantile Paralysis, Inc.

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¶Associate professor of pediatrics, University of Minnesota Medical School.

¶This vaccine, which was prepared from egg cultures of influenza A (PR 8 and Wells strains) and B (Lee strain) viruses by erythrocyte adsorption and elution was kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

||This vaccine, which was prepared from egg cultures of influenza A (PR 8 and Wells strains) and B (Lee strain) viruses by calcium phosphate adsorption, was kindly supplied by Parke, Davis and Company, Detroit, Michigan.

Vaccine 2 caused little or no immediate pain. The local reaction was measured and palpated at intervals, and although there was considerable variation, the following general observations were made twenty-four hours after the injection of vaccine 1: there was a small area (1 or 2 cm) of erythema,

TABLE 2 Frequency of Systemic Reactions to Influenza Vaccine

VACCINE	DOSE cc	TOTAL NO OF SUBJECTS	SUBJECTS WITH REACTIONS	
			NO	PERCENTAGE
1	0.5	39	11	28
2	0.5	48	3	6
1	1.0	49	10	20
2	1.0	48	8	17

which was slightly swollen and indurated and moderately tender. At forty-eight hours there was usually minimal or no local reaction remaining. Twenty-four hours after the administration of vaccine 2 there was an area of erythema, which, on the average, was significantly larger (2 to 10 cm) than that caused by vaccine 1. Also, the local site was usually more swollen and indurated, and in a

quent, reactions were observed with vaccine 1. The least number of systemic reactions occurred with 0.5 cc of vaccine 2. A convulsion occurred in a one-year-old girl who received 1 cc of vaccine 1.

No unquestionably positive reaction was observed in any of the 60 children who were given skin tests. Difficulty in interpreting skin tests with the undiluted vaccine was encountered because of the irritative properties of the formalin contained in the material used. (None of these subjects are included in the titer studies.) Curphey<sup>3</sup> has reported a fatal allergic reaction to influenza vaccine. Ratner and Untracht<sup>4</sup> cited several allergic reactions and recommend that all patients be tested with 0.02 cc of the undiluted vaccine before vaccination. Protamine-precipitated vaccine,<sup>5</sup> like that of calcium phosphate adsorbed, apparently contains less allergenic substance than the vaccine prepared by erythrocyte adsorption. A newer vaccine prepared by centrifugation<sup>6</sup> is said to be virtually free of substances causing allergic reactions.

### Antibody Titers

The increase in the antibody titer is indicated by the ratio of the late to the early value rather than

TABLE 3 Frequency Distribution of Titer Ratios

VACCINE	DOSE cc	INFLUENZA VIRUS	SUBJECTS WITH INCREASE OF LATE OVER EARLY TITER				TOTAL NO OF TITER PAIRS	GEOMETRIC MEANS OF INCREASES
			LESS THAN 2 FOLD	2 TO 3.9 FOLD	4 TO 7.9 FOLD	8 TO 50 FOLD		
1	0.5	A	14	3*	7	3	27*	2.4 fold
2	0.5	A	14	5	1	2	22	3.5 fold
1	0.5	B	8	8	6	5	27	1.9 fold
2	0.5	B	9	7	2	4	22	2.9 fold
1	1.0	A	11	7	3	1	22	2.1 fold
2	1.0	A	5	3	4	2	14	4.1 fold
1	1.0	B	4	6	6	5	21	3.0 fold
2	1.0	B	1	2	3	7	13	7.8 fold
(Control)		A	30	0	0	0	30	1.0 fold
(Control)		B	30	0	0	0	30	1.0 fold†

\*Of the 27 titer pairs against influenza A in the group receiving 0.5 cc of vaccine 1, there were 3 with late titers showing an increased range of 2 to 3.9 fold over the early titers.

†1.0 fold represents no increase in the late over the early titer.

few subjects the whole upper arm was tender. At the end of forty-eight hours a definite subcutaneous nodule had formed in most of the subjects receiving vaccine 2. This was still present thirty days later in a few cases.

### Systemic Reactions

The number of systemic reactions is recorded in Table 2. The ages of the children with reactions ranged from thirteen months to nine years in the group given 0.5 cc of vaccine 1, three to thirteen years in the group given 0.5 cc of vaccine 2, sixteen months to sixteen years in the group given 1 cc of vaccine 1 and two to fifteen years in the group given 1 cc of vaccine 2. The principal reactions were headache, restlessness and wakefulness. In general it was concluded that severer, as well as more fre-

quent, reactions were observed with vaccine 1. Table 3 shows the frequency distribution of all the cases in terms of the number of fold increase of the late titer over the early titer (late to early ratio).

In view of the fact that the titers increase in a geometric fashion, the geometric mean was employed in the group comparisons, and the statistical calculations were made on the basis of logarithms. The geometric means for the titer increases are included in Table 3. All the means in the groups receiving vaccine were significantly higher than those in the control group. Except for the mean increase of 7.84 against the virus of influenza B in the group receiving 1 cc of vaccine 2, in which the number of patients was too small and the range of values too great to justify an accurate comparison, there was no significant difference

between the groups. For example, 1 cc of a vaccine was no better than 0.5 cc of the same vaccine, nor was vaccine 1 better than vaccine 2 from this point of view. There did not appear to be any differences in the titer response of the younger compared to the older children. The titers against the virus of influenza B were generally higher than those against the virus of influenza A.

### DISCUSSION

The subjects in our study were not exposed to an epidemic of influenza, so that the value of the vaccinations was not tested clinically. A fairly consistent rise in antibody titers was demonstrated in the majority of the vaccinated group as opposed to the controls. Henle, Henle and Stokes<sup>7</sup> have shown greater protection against the disease in the persons with the high titers. The majority of the subjects whose titers failed to rise appreciably (less than twofold) had high initial levels.

All the inoculations were given subcutaneously. Van Gelder and his associates<sup>8</sup> concluded that the intracutaneous route produced better titer responses. No subject in our study received more than one injection. The antibody level reached after one dose was as high as that observed after two doses according to a study reported by Hare and his co-workers.<sup>9</sup>

The second blood sample was drawn after fourteen days in all subjects. These titers probably did not represent the maximum level in each case because of varying host responses as well as the differences in vaccines used.

In our experience, the vaccines employed were safe for infants and children in the doses employed, and with one exception, in which a large dose was given to a one-year-old child, no severe reactions were observed in the 245 subjects. The question of the use of influenza vaccine in the practice of medicine remains for the individual physician to answer. Certainly, it may be offered as giving protection of some degree to most persons, since its value has now been attested by several reports, including that of the Army Influenza Commission.<sup>10</sup> The administration of any vaccine entails an occasional unfavorable reaction. Whether or not this militates against its use in practice cannot be decided here, but its value as a public-health measure can hardly be questioned when the morbidity and mortality figures in large cities after influenza epidemics are studied. The uncomplicated disease except for pandemics probably is not responsible for death, but it is one of the common precursors of

pneumonia, which takes its toll after every influenza epidemic. The pandemics of influenza recorded in medical history have been responsible for more deaths than any scourge known to man. One of the probable causes of pandemics is a world-wide susceptibility. It seems possible that extensive use of influenza A and B vaccine will offer man some protection against pandemic as well as epidemic influenza and against the high mortality associated with this disease.

### SUMMARY

A comparative study of reactions, doses and antibody titers has been made with two different vaccines against influenza A and B in infants and children.

The temperature elevations were significantly higher with vaccine 1 than with vaccine 2, although the dose of the vaccines did not appear to make any appreciable difference. Vaccine 2 caused more local reactions, such as swelling and tenderness at the site of inoculation, whereas the systemic reactions appeared to be more intense with vaccine 1.

A definite increase in the antibody titers was demonstrated in the majority of the vaccinated subjects as compared to the controls, but no significant difference between the vaccines was observed.

There was no significant difference between the titers obtained with 0.5 cc and 1 cc of the same vaccine. Children under three years of age, in our opinion, should not be given more than 0.5 cc of vaccine.

The decision whether or not to use influenza vaccine is left to the individual physician.

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ACUTE MENINGITIS CAUSED BY *NEISSERIA SICCA*\*

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THE gram-negative diplococci such as *Neisseria catarrhalis* and *N. sicca*, commonly found in the pharynx, rarely cause meningitis. However, upon occasions they have been proved to be the sole cause of the disease.<sup>1-10</sup> The following case of meningitis due to *N. sicca* was proved by culture and serologic examination §

R. L., a 6½-year-old boy, entered the hospital on January 20, 1947, with a history of sore throat, frontal headache, fever and vomiting of 24 hours' duration. The temperature had risen to 104°F, the headache had increased in severity and he had developed a stiff neck a few hours before admission. The patient had received several doses of sulfadiazine at home, but most of this had been lost in the vomitus.

The past and family histories were noncontributory except for left internal strabismus since infancy.

Physical examination revealed a well developed and well nourished child, who was drowsy but conscious and co-operative. There were no abnormal eye findings except for the left internal strabismus. The fundi were normal. Definite spinal and nuchal rigidity were elicited. The mucous membrane of the throat was somewhat inflamed. The ears were normal. The posterior cervical lymph nodes were slightly enlarged. No petechiae were noted. A bilateral Kernig reflex was present. The blood pressure was 100/70.

Examination of the blood showed a red-cell count of 3,930,000 and a white-cell count of 15,200, with 86 per cent neutrophils, 12 per cent lymphocytes and 2 per cent eosinophils. A blood culture was negative, as was a tuberculin patch test. An x-ray film of the chest was normal. The blood sulfadiazine level ranged from 9 to 15 mg per 100 cc. A lumbar puncture was done and 10 cc of cloudy spinal fluid, under increased pressure, was obtained. The initial pressure was equivalent to 280 mm of water, the dynamics were normal. Examination of the spinal fluid disclosed a white-cell count of 4150, with 84 per cent polymorphonuclear leukocytes, 16 per cent lymphocytes and a total protein of 80 mg, sugar of 83 mg and chloride of 720 mg per 100 cc. A direct smear demonstrated many pus cells but no organisms, a culture showed *N. sicca*.

As soon as the diagnosis of meningitis had been established the patient was given sodium sulfadiazine intravenously and penicillin intramuscularly. Because the previous vomiting had resulted in some dehydration, 5 per cent glucose in physiologic saline solution with 1/6 molar lactate was given intravenously. In the evening of the 2nd hospital day, the urine was noted to be grossly bloody, and sodium sulfadiazine was therefore discontinued. Streptomycin (125,000 units every 3 hours) was started, and 1/6 molar lactate was continued intravenously to keep the urine alkaline — 24 hours later the urine was free of blood.

On the day after admission the patient showed considerable improvement, and he was able to retain food. Penicillin was given intrathecally (5000 units in 5 cc of physiologic saline solution) on the 2nd and 3rd days. The urine contained red cells on the 3rd hospital day but was normal thereafter. On the 4th hospital day, there were no clinical signs of meningitis. Streptomycin was discontinued, and at that time oral glucosulfadiazine was given without any further untoward effect. The patient continued to improve. Penicillin was discontinued on the 9th, and glucosulfadiazine on the 11th hospital day. The spinal fluid on discharge was

clear, with 4 white cells per cubic millimeter, 100 per cent lymphocytes, a sugar of 49 mg per 100 cc and a total protein of 36 mg per 100 cc, culture was negative.

Serum agglutination with *N. sicca* demonstrated a positive titer in a dilution of 1:384 (control, negative) 12 days and one of 1:384 (control 1:96) 61 days after the onset of the acute illness. The titer was negative for both patient and control 154 days after the onset.

## DISCUSSION

The initial diagnosis in this case was meningococcal meningitis, in view of the presence of clinical meningitis with cloudy spinal fluid, which on direct smear showed many pus cells but no organisms. The diagnosis was further strengthened by the report of the presence of a gram-negative diplococcus obtained from the culture of the spinal fluid. However, the laboratory soon reported that the organism isolated did not agglutinate with any of the strains of meningococci available. Subsequently, this organism was identified by the laboratory of the Worcester Public Health Department and confirmed by the laboratory of the Massachusetts Department of Public Health as *N. sicca*.

The possibility of contamination of the spinal fluid was entertained, but on inquiry it was found that this organism is a very rare contaminant.<sup>11</sup>

The question of determining whether the patient had developed immune bodies to this organism was then investigated. Because *N. sicca* tends to clump spontaneously in the presence of physiologic saline solution, the antigen was prepared by a special method to minimize this phenomenon. The organism was grown on nutrient agar slants and incubated at 35°C for forty-eight hours. The slants were washed off with tap water as a precautionary measure to avoid automatic precipitation of the organism. The harvest was collected and ground up with fine sand,<sup>12</sup> and the suspension was allowed to stand for one hour. The supernatant fluid was decanted through cotton, and the suspension diluted with tap water to a No. 8 McFarland nephelometer standard of approximately 2,400,000,000 organisms per cubic centimeter. The antigen was then killed at 60°C for one hour. No preservative was added. The routine slow macroscopic tube agglutination test was used, as described by Kolmer and Boerner.<sup>13</sup> Inasmuch as there was a small but definitely noticeable amount of antigen precipitation in tap water, a positive reaction was assigned only to tubes that showed marked clearing with the formation of large flakes.

It will be noted that twelve and sixty-one days after the onset of acute symptoms, the organism

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<sup>13</sup>Suggested by Dr. Raymond H. Goodale, pathologist, Worcester City Hospital.

was agglutinated by the patient's serum in a dilution of 1:384. Approximately five months after the illness the titer had dropped to a normal level. The control serums were presumed to be normal and were obtained from men between the ages of twenty and twenty-three years. The finding of a titer of 1:96 in one of the control serums cannot be definitely explained, except by the fact that the control subject may have had a recent infection with *N. sicca*.

On review of the literature it was found that meningitis due to *N. sicca* has been reported only in the course of an endocarditis caused by this organism.<sup>5-7, 10, 12</sup> In the 5 reported cases of endocarditis, symptoms of meningitis occurred in 3, and a positive spinal-fluid culture was found in 1.<sup>7</sup> All these cases of endocarditis terminated fatally except 1 in which recovery followed the use of heparin and sulfapyridine.<sup>6</sup>

Several cases of meningitis caused by *N. catarrhalis* have been reported<sup>11, 9</sup> and also some cases caused by atypical *Neisseria*.<sup>2, 3, 4, 8, 10</sup> The comparative rarity of meningitis caused by this group of organisms suggests a low pathogenicity but modifies the older concept of this group as non-pathogenic.<sup>14</sup>

#### SUMMARY

A case of acute meningitis caused by *Neisseria sicca* is reported. The organism isolated was identified by two different laboratories. An attempt was made to determine the titer of antibodies in the

patient's serum, cultures of the organism being used as the antigen. Although the serologic method available was not entirely satisfactory because of the characteristics of this organism to clump spontaneously, significant titers indicating antibody formation were obtained. Approximately five months after the onset of the acute disease, the titer had dropped to a normal level.

It is believed that this is the first straightforward case of acute meningitis caused by *N. sicca* and uncomplicated by any other infectious process such as endocarditis described in the literature.

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## MEDICAL PROGRESS

### CANCER

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AS a result of public interest, large sums of money have become available in the field of cancer, from state and federal sources and from charitable foundations, and it seems probable that the interest and funds will continue for a long time. The money has been used for stimulation of research, for cancer education among the laity and the medical profession and for direct service to the patient in the form of improved diagnostic and therapeutic facilities.

#### RESEARCH

The literature of laboratory cancer research has become so voluminous that it is virtually impossible for anyone to undertake to digest it all. The Fourth International Cancer Research Congress presented representative contributions in all the principal fields of investigation. Cowdry's<sup>1</sup> recent summary of the Congress ably recapitulates the major fields of interest.

#### EDUCATION

##### *Undergraduate*

Although a considerable part of a medical-school curriculum deals with cancer, and with basic sciences essential to an understanding of cancer, it is true that in many medical schools there has been little or no attempt to correlate the various components in such a way as to give the student a coherent conception of cancer. A committee of the National Advisory Cancer Council has urged the desirability of co-ordinating the teaching of cancer in medical schools, offering financial support for schools presenting acceptable plans of instruction. Several schools have already adopted the recommendations of the committee, and it is anticipated that others will recognize the merits of the proposals.

##### *Graduate*

Fellowships offered by the National Advisory Cancer Council are intended to train men at the resident level to be cancer specialists. The rather rigid requirements of training in surgery, radiology and pathology make it difficult for many hospitals to fit these fellowships into existing resident training programs. In addition, the fellowships come into conflict with the requirements of many of the specialty certification boards. Some relaxation and

elasticity of the program would probably result in better training of more men.

The American College of Surgeons, at the annual clinical congress and in the sectional meetings, offers special sessions and symposia in cancer. These meetings bring to a large audience a condensed review of recent important advances in the cancer field. The series of special articles appearing in the *Journal of the American Medical Association*,<sup>2</sup> with the co-operation of the American Cancer Society, is designed to bring a concise presentation of cancer subjects to the general practitioner. These articles will be assembled in a book, which will assure their preservation.<sup>3</sup> The announcement of a new journal *Cancer*, under the sponsorship of the American Cancer Society, to include a thorough abstract section in addition to original contributions, is welcome news to all who are working in this field.

##### *Public*

Lay education in cancer has been promoted by various groups, notably by the Women's Field Army of the American Cancer Society. There can be no question that as a result of such education, many patients seek medical advice earlier than they would have done otherwise. They are also likely to require a more thorough examination from their physician. Indeed, the demands of the laity have emphasized the necessity for improved cancer teaching for the profession. The public interest stimulated by lay education has in large measure helped to make available the funds referred to above, and to some degree has given the laity a voice in the projects for which the money is used. The public demand has also been responsible for the development of detection clinics.

#### DETECTION CENTERS

It is a basic postulate that the earlier a cancer is detected and treated, the greater is the likelihood of cure. It is also true that the earliest stages of most cancers give rise to no symptoms. Thus, it would be desirable to have some test to which the apparently healthy person could be submitted that would detect cancer in its earliest stages. The only present test that can be employed is a complete and thorough examination. The more thorough the examination, the greater is the likelihood that cancer will be detected in its early stages. Practical considerations of time, personnel and expense impose

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limitations on the thoroughness of the examination. It is apparent that the initial examination must be relatively brief and inexpensive, and that this preliminary screening may be expected to segregate for more extensive study the group most likely to show positive findings.

In regular medical practice the most significant finding on screening is the presence of a symptom or symptoms. Indeed, a patient in general exercises this screening test and consults a physician or goes to a clinic because of a symptom. The physician can then carry out the more thorough investigation necessary to discover the cause of the symptoms. In doing so, he may uncover cancer or some other disease. Without the stimulus of symptoms to be explained, examinations may become perfunctory or routine. Statistics must be available regarding the number of cases of cancer found during the routine physical examinations of applicants for life insurance or of men selected for military service. Statistics are available concerning the expected incidence of cancer in various age groups at a given time.<sup>4</sup>

In response to public pressure, under the sponsorship of various foundations, numerous centers have been established for the detection of cancer. The American College of Surgeons has defined standards for these centers and gives approval to those complying with the standards.<sup>4</sup> Most of the centers report a much higher incidence of cancer than the calculated expected frequency.<sup>6</sup> It is probable that this is due to the inclusion of a large number of persons who are not in fact free from symptoms, and that the centers are serving to this extent as cancer clinics rather than as detection centers.

The centers also reveal a very great number of other conditions requiring medical treatment.<sup>7</sup> These findings may be compared with the number of rejections for physical reasons of men selected for military service. Proponents of the centers consider that many of the nonmalignant conditions encountered are precancerous, and that prompt attention to them prevents the development of cancer. This viewpoint involves a rather broad concept of precancerous conditions.

Although it is premature to evaluate cancer-detection centers, the experiences should be dispassionately reviewed from the standpoint of expense of operation in relation to cases found at a significantly early stage. Follow-up studies of the cases with negative findings should give information regarding the number of cases overlooked. It may well be found that greater numbers of early cancers can be found with less expense of time and money, by intensified education of the laity to report early symptoms and of the medical profession to evaluate these early symptoms.

#### DIAGNOSIS

Interest in cytologic methods of diagnosis from smears continues unabated,<sup>8-11</sup> although many

orthodox pathologists preserve a commendable reluctance to accept the findings without reservation.<sup>12</sup> The application of this technic to permit early evaluation of the efficacy of radiation treatment of carcinoma of the cervix, proposed by Graham,<sup>13</sup> may prove to be valuable in the selection of cases requiring surgical intervention. A series of 280 aspiration and punch biopsies was reported by Ellis,<sup>14</sup> with "useful results" in 63 per cent. Meatheringham and Ackerman<sup>15</sup> reported 300 aspiration biopsies on lymph nodes. In 69 aspirations no lymphoid tissue was obtained. A positive diagnosis of carcinoma was made in 147 specimens, and cancer subsequently developed in 32 cases in which the aspiration specimen was negative. Several authors express a warning against aspiration biopsy in possibly operable lung tumors, because of the danger of pleural implantation. Isaacson and Rapoport<sup>16</sup> reported a series of 34 cancer patients who presented an eosinophil count of more than 10 per cent. It is not generally realized that this degree of eosinophilia may be caused by cancer. In 90 per cent of cases multiple metastases were present.

#### LYMPHATIC SPREAD

There has been considerable interest in recent years in amplifying and confirming knowledge of the pathways of lymphatic spread. The brilliant studies of Gilchrist and David<sup>17</sup> on the lymph-node metastases of carcinoma of the colon and rectum have greatly influenced the concept of the radical operations for dealing with these cancers. Similar methods of study were employed by Coller, Kay and MacIntyre<sup>18</sup> in cancer of the stomach, colon and rectum. Sweet<sup>19</sup> has contributed to knowledge of the lymphatic spread of carcinoma of the esophagus. Warren and Tompkins<sup>20</sup> have drawn attention to the correlation between prognosis and the numerical extent of lymph-node metastases. Whereas it is generally conceded that lymph-node involvement is usually embolic rather than by permeation, it is evident that the concept of permeation frequently influences the plan of operation, and it remains true that removal of the regional lymphatic vessels en bloc along with the primary focus is an ideal cancer operation when it is feasible.

#### SURGICAL TREATMENT

Critical review of autopsy material discloses that in many cases death from cancer is due to the local extension of the disease, with interference with the functions to adjacent normal organs, rather than to widespread metastatic involvement. Realization of this fact, in conjunction with the general lowering of mortality and morbidity after radical surgery, has led to increasingly radical operative procedures to cope with advanced stages of local disease. Although these operations are too recent to permit evaluation of long-term cures, they offer the possi-

bility of cure in many cases hitherto regarded as inoperable, and in most cases find justification at least as effective palliative procedures. While Brunschwig has written extensively on this subject, the tendency is evident in almost all fields of cancer surgery.

### ORAL CANCER

No single report indicates the trend in the field of oral cancer, but many surgeons are reviving the concept of a one-stage operation for lesions of the tongue, floor of the mouth and cheek, with simultaneous neck dissection and, when necessary, resection of the jaw. These operations can be applied to some cases considered inoperable by conventional standards. Since the procedures are based upon the concept of spread by permeation, which is not the usual method of lymphatic involvement from these cancers, in many cases they show no advantage over the two-stage operations currently practiced. In addition, in coping with inoperable intraoral lesions, they must demonstrate results more satisfactory than those now obtainable by intensive radiation. Although these radical operations undoubtedly have a place, it is likely that their field of employment will be a restricted one.

### CERVICAL-LYMPH-NODE METASTASES

There has been increased willingness on the part of certain surgeons to carry out radical neck dissections bilaterally, with a short interval between the two sides. This procedure involves sacrifice of both internal jugular veins, as well as the anterior and external jugular veins, and is not without danger of causing cerebral damage. In most cases it is probably safer to preserve the internal jugular vein on one side, and it is usually possible to do so. Sugarbaker and Gilford<sup>23</sup> recently drew attention to the combination of neck dissection and jaw resection in cases in which lymph nodes present fixation to the mandible. This procedure has been employed in many clinics, and the dangers of postoperative complications of shock, hemorrhage, sepsis and pneumonia have diminished.

### CARCINOMA OF THE LARYNX

New et al<sup>24</sup> have reported the excellent results obtained by radical surgery in carcinoma of the larynx. Whereas it is true that many of the early cases are amenable to radiation therapy, there is agreement that laryngectomy is the procedure of choice in more advanced cases,<sup>25, 26</sup> and there is evidence that subradical surgical procedures are more effective than radiation in most early cases.

The possibility of training patients in esophageal use of the voice makes laryngectomy more acceptable. Brunschwig<sup>27</sup> has carried out very radical laryngectomy for advanced disease, removing regional lymph nodes and any other structures that may be implicated in the spread of the disease.

### CARCINOMA OF THE LUNG

Most authors recognize the desirability of removing enlarged lymph nodes in the vicinity of the hilus, along with the entire lung, in carcinoma of the lung. In addition surgeons have not hesitated to resect invaded areas of pericardium, parietes or other adherent structures. Although no cures have been obtained by these radical extensions, the operations at least fulfill the desideratum of leaving no obvious disease behind.<sup>28, 29</sup>

There has been increased recognition of the feasibility and desirability of carrying out pulmonary resection for solitary metastasis of sarcomas and carcinomas, and occasionally long-term arrests or even cures are effected.<sup>30</sup>

### CARCINOMA OF THE ESOPHAGUS

The extent of operations for esophageal carcinoma has increased, with better understanding of the intramural and lymphatic spread of the disease. In this field also Brunschwig and Camp<sup>31</sup> have described a very radical extirpation of the total cervical esophagus. Garlock<sup>32</sup> and Sweet<sup>33</sup> have contributed to elucidation of the technical problems of resections.

### CARCINOMA OF THE STOMACH

Coller's<sup>34</sup> studies of metastases have emphasized the desirability of more radical operations for carcinoma of the stomach. Longmire<sup>35</sup> and Wahren<sup>36</sup> have advocated total gastrectomy as a better operation for cancer than subtotal gastrectomy. However, the mortality from total gastrectomy still remains relatively high,<sup>36</sup> and the survivors, even those who are cured of cancer, may be significantly impaired in health.<sup>36</sup> All authors emphasize the urgent need for earlier recognition<sup>37</sup> and for a radical approach to the problem of gastric ulcer.<sup>38, 39</sup>

### MISCELLANEOUS ABDOMINAL CARCINOMAS

In the field of multiple and apparently inoperable abdominal carcinomas, Brunschwig<sup>40, 41</sup> has reported a brilliant series of radical improvisations, as well as modifications of operative technic in carcinomas of the pancreas and duodenum.<sup>42</sup> Resections of the liver for primary carcinoma were reported by Hoyne and Kernohan<sup>43</sup> and by Duckett and Montgomery.<sup>44</sup> Rabinovitch et al<sup>45</sup> described a series of sarcomas of the intestinal tract. Ehrlich and Hunter<sup>46</sup> reviewed the experience of the Army Institute of Pathology in tumors of the gastrointestinal tract.

### CARCINOMA OF THE RECTUM

The same unwillingness to accept local fixation as a contraindication to radical operation applies to carcinoma of the rectum. Bricker<sup>47</sup> presented a number of cases in which parts of the male genitourinary tract were included in the resection, even to the extent of total removal of the bladder,

prostate and vesicles, with transplantation of the ureters into the proximal portion of the bowel. In the female patients it is not unusual to include the uterus and posterior vaginal wall in the resection.

### CARCINOMA OF THE CERVIX

There has been a revival of interest in the radical operation for carcinoma of the cervix,<sup>43</sup> based on the lowered mortality and recognition of the inadequacy of radiation in the control of lymph-node metastases. This operation has also been extended to include certain cases with local invasion of the bladder or rectum or both.<sup>44</sup> The successful outcome of such an operation—total cystectomy, total hysterectomy, lymph-node dissection, abdominoperineal resection of the rectum, vulvectomy, vaginectomy, and bilateral ureteral transplantation—is eloquent testimony to improved technology in surgery.

### CARCINOMA OF THE BREAST

Haagensen<sup>45</sup> has returned to the classic Halsted amputation, with wide skin removal, thin skin flaps and routine skin grafts, in the operation for carcinoma of the breast. Most students believe that this elaborate and meticulous operation is not necessary. Differences in results from various clinics are often attributable to differences in the criteria of operability. Ducuing<sup>46</sup> employs a more radical operation than that usually carried out in this country, removing the fascia of the subscapular muscles and the anterior digitations of the serratus magnus muscle and the subclavius muscle, along with the thoracodorsal and long thoracic nerves. Pickrell et al.<sup>47</sup> described techniques employed in localized resections of the thoracic wall in dealing with operative-field recurrences.

### SARCOMA OF THE EXTREMITIES

Gordon-Taylor and Patey<sup>48</sup> presented a further review of their series of interminominoabdominal amputations, chiefly performed for sarcoma of the upper portion of the thigh and pelvis. Pack and Ehrlich<sup>49</sup>,<sup>50</sup> have also presented a series of radical amputations, in some cases combined with regional lymph-node dissections, for a variety of advanced malignant conditions. Again on the basis of the theory of lymphatic permeation, Pack et al.<sup>51</sup> stated, "In the lower extremity for primary melanoma of the foot metastatic to inguinal and femoral lymph nodes, we resort to a hip joint disarticulation combined with a retroperitoneal dissection of the iliac and obturator nodes." This procedure appears to be excessively radical unless the authors intended to restrict it to certain cases of advanced disease. Haggart<sup>52</sup> reported a series of radical shoulder-girdle amputations in the treatment of primary malignant tumors of the humerus.

### MALIGNANT LYMPHOMA

Hellwig<sup>53</sup> reported a series of cases of localized malignant lymphoma in which radical surgery was employed, with five-year cures in a significant number of cases.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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### CASE 34171

#### PRESENTATION OF CASE

A thirty-year-old man, a store clerk, entered the hospital with a complaint of pain in the stomach.

Six months prior to entry the patient noted a dull, heavy, nonradiating, epigastric pain, which occurred in the morning and after meals. It was relieved in part by alkalies and warm milk. There was no nausea or vomiting and no tarry stools, and only a rare stool contained bright-red blood. There had been no anorexia or weight loss. About a week before admission a dull, constant, nonradiating pain in the left flank suddenly developed. Two days prior to admission there was a dull, aching pain in the hypogastrium. This was intermittent in character and resembled the epigastric pain.

Physical examination showed a well developed and well nourished man who was moderately distressed because of hypogastric pain. The lungs were clear to percussion and auscultation. The heart was not enlarged, and no murmurs were heard. There was tenderness in the abdomen to deep pressure, localized mainly just to the left of the umbilicus. Pressure on that area also produced pain in the

back. There was no rebound tenderness. In addition, there was definite costovertebral-angle tenderness on the left and in the region of the left kidney. The liver and spleen were not palpable. There was thought to be a group of matted lymph nodes at the base of the left jugular vein.

Examination of the blood disclosed a hemoglobin of 13 gm and a white-cell count of 8200, with 77 per cent neutrophils. The urine was normal. A stool specimen gave a negative guaiac reaction. The total protein was 7.4 gm, the nonprotein nitrogen 27 mg per 100 cc, the chloride 98 milliequiv per liter, and the serum amylase 16 units.

On the day of admission a gastrointestinal series revealed a 5-cm filling defect on the greater curvature in the prepyloric region. No ulceration was observed, and peristalsis did not pass through the area. A smear and gastric washings showed no malignant cells. An intravenous pyelogram performed on the third hospital day was not entirely satisfactory because of gas and fecal material in the overlying bowel, but demonstrated a delayed secretion of the dye on the left, with a moderate degree of hydronephrosis and hydroureter. Two days later a retrograde pyelogram again showed a left hydronephrosis and some degree of obstruction to drainage of the opaque medium. On the sixth hospital day a gastroscopy showed the greater curvature to be distorted by red, edematous rugae. There appeared to be spasm over this area, and no peristalsis was present. There was a superficial ulceration on the lesser curvature, which measured 1 mm in depth and 1 cm in diameter. The appearance described extended about halfway up the body of the stomach and then ended rather abruptly. On the eighth hospital day the patient vomited reddish-brown material and had severe, colicky pain in the left flank that persisted.

On the twelfth hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR DANIEL S ELLIS It seems to me that it is very clear that this patient had disease involving the stomach and left urinary tract, and I judge that the same disease involved both organs and that it was a malignant process of some kind. I do not know what kind of operation was performed—whether he had a biopsy or whether he was operated on with the idea of attacking the stomach or left urinary tract. Perhaps the x-ray films will help in determining the nature of the lesion in the stomach, and also reveal the location of the obstruction in the left urinary tract.

DR STANLEY M WYMAN Examination of the stomach shows the antrum and prepyloric region to be constantly deformed. On the greater curvature there is a constant pressure defect, which elevates the antrum and prepyloric region. The mucosal folds in the lesser and greater curvatures appear unusually thick and prominent. One can see no definite destruction of the mucosa, however. The duodenal loop is not remarkable, but there is deformity of the cap consistent with an old ulcer. The two films from the pyelogram show a slight degree of hydronephrosis on the left with blunting of the minor and major calyces, and widening of the ureter and pelvis. The ureter is traced to the body of the fourth lumbar vertebra. There is no obstruction to that point, and there are no visible stones to account for the dilatation. A single film taken from the retrograde examination shows more clearly the hydronephrosis, which has a generalized character with some delay in the passage of dye at the ureteropelvic junction. No definite obstruction of the ureter can be seen. The kidney outline cannot be adequately detected. The kidney is not displaced in position, and there is no evidence of a pressure defect on the kidney itself. The lung fields and heart are not remarkable.

DR ELLIS Is there any evidence of a soft-tissue mass at the base of the neck?

DR WYMAN No, not in this one film.

DR ELLIS It seems to me that there is no question that if we can ever interpret symptoms as being typical of certain diseases, this patient had a peptic ulcer or ulceration in the stomach, and the original symptom of a dull, nonradiating epigastric pain occurring postprandially early in the morning and relieved by alkalies and warm milk is that of an ulcerating lesion in the stomach. The pain seemed to change very definitely and became hypogastric and related to the region of the left kidney. As far as I am able to determine there are no other clues.

I suppose that a simple peptic ulcer can be fairly well ruled out on the basis that both the gastroscopist and the radiologist who examined the patient thought that there was an extensive lesion involving the lower part of the stomach in the prepyloric

region. Therefore, I believe that this patient had a malignant lesion involving both the stomach and the retroperitoneal lymph nodes and the left ureter, causing hydronephrosis. Such a condition must have been a carcinoma or a lymphoma of some kind. On the law of averages a patient thirty years old ought not to have carcinoma of the stomach, and it is much more likely that he had a lymphoma. The types of lymphomatous disease possibly involving the stomach and the lymph nodes are reticulum-cell sarcoma, lymphosarcoma and, much less likely, Hodgkin's disease. Still another possibility is tuberculosis, of which there seems to be no indication. If this patient's symptoms were first related to the stomach, I think that he had a prepyloric lesion, which was primary in the stomach and metastasized, involving the left urinary tract, causing pressure on the left ureter, with secondary hydronephrosis, and I shall put lymphosarcoma as the first choice. Having had two cases of renal-cell carcinoma before me today, I suppose I am on the spot to say that this is a third case of renal-cell carcinoma, since things usually come in threes. I think that a primary renal tumor with metastases involving the stomach would be less likely than the other way around—that this was a primary carcinoma of the stomach with metastases involving the left urinary tract. I do not believe that this was a scirrhus type of cancer such as one sees in linitis plastica, although it was certainly an infiltrating lesion from the description.

I shall conclude by saying that this man had lymphosarcoma, primary in the stomach, with metastases involving the retroperitoneal lymph nodes and causing partial obstruction and increasing obstruction to the left ureter. And if he really had lymph nodes in the neck I shall interpret them as further evidence of that diagnosis. If he had Hodgkin's disease or leukemia, I would expect to have some clue from the blood smears, but there are none recorded for me to base such a diagnosis on.

DR EDWARD B BENEDET I do not remember this case, but from the description I do not believe it is correct to say that I saw the prepyloric area and described the region of the antrum. As I read the description given, there was an ulcer on the lesser curvature, probably in the body of the stomach.

DR ELLIS It is reported by you and the roentgenologist that no peristalsis was seen in the lower portion of the stomach.

DR BENEDET It probably means that I did not see the antrum and pylorus.

DR ELLIS From the x-ray studies and the way I read this summary I interpret them to signify involvement of the lower end of the stomach by an infiltrating type of lesion.

## CLINICAL DIAGNOSIS

Lymphoma involving the stomach wall and retroperitoneal tissues?



## DR ELLIS'S DIAGNOSES

- Infiltrating malignant tumor of stomach, probably lymphosarcoma, with metastases to retroperitoneal nodes
- Left hydronephrosis secondary to metastatic involvement of left ureter near left renal pelvis

## ANATOMICAL DIAGNOSES

- Mucous carcinoma of stomach, signet-ring type*
- Metastases to mesenteric and retroperitoneal lymph nodes
- Obstruction of left ureter from external pressure
- Hydronephrosis, left
- Congenital hypoplasia of kidney, right

## PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY This patient was explored by Dr Gephart and a large tumor mass found that involved half the stomach, a portion of the omentum and extended down to the region of the left kidney, which appeared to be entirely involved in the same mass. A biopsy of the tumor showed that it certainly was not lymphoma. It was an epithelial tumor with large vacuolated cells, somewhat suggestive of but by no means typical of renal-cell carcinoma, it was so reported.

The patient was transferred to another hospital, where he died a few days later. The post-mortem examination, kindly made available to us by Dr John J Larkin, the pathologist, showed a scirrhous signet-ring carcinoma of the pyloric half of the stomach. A shallow ulceration was present on the anterior wall. The tumor had grown through the gastrocolic omentum to involve the colon and had metastasized extensively in the mesenteric and retroperitoneal lymph nodes. A group of these enlarged nodes surrounded the left ureter, obstructing it by pressure and so producing a hydronephrosis. The right kidney was very small, perhaps congenitally hypoplastic, and also showed hydronephrosis. The right ureter was dilated.

## CASE 34172

## PRESENTATION OF CASE

A forty-seven-year-old woman entered the hospital complaining of pain in the left leg.

She was well until one year prior to admission, when she developed pains in the neck and back, had a gradual loss of energy, easy fatigability and an increased appetite, and had frequent loose bowel movements associated with an urgent gastrocolic reflex. There was slight exaggeration of all these

symptoms in more recent months. Six months before entry she had a barium enema, which was said to have been negative. Two weeks prior to admission the patient had several short chills and ran a slight fever. Five days prior to admission she developed discomfort in the left calf, which persisted until entry. She also had some transient pain in the right leg and during that time ran a temperature of 101°F. Upon entry she was unable to walk because of severe pain in the left calf. She gave no history of hemoptysis, nausea, vomiting or tarry stools.

Physical examination revealed a very obese woman, weighing 230 pounds. There was moderate tenderness in the left leg, extending from the ankle to 8 cm above the knee. The left calf was swollen from 1 to 2.5 cm more than the right calf. There was a positive Homans's sign in the left leg, and there were distended veins over the dorsum of the left foot. The rest of the physical examination was essentially negative.

The temperature was 99.5°F, the pulse 95, and the respirations 18. The blood pressure was 145 systolic, 90 diastolic.

Examination of the blood disclosed a hemoglobin of 13 gm and a white-cell count of 10,700, with 82 per cent neutrophils. The urine was normal. The sedimentation rate was 38 mm in one hour. The prothrombin time was 24 seconds (control, 17 seconds).

The patient was immediately started on a course of anticoagulant therapy, beginning first with heparin and then changing to dicumarol. A chest film was interpreted as negative for previous pulmonary infarcts. The fever continued, the temperature spiking to 101°F in the next few days. On the second hospital day a sharp pain developed in the left lower anterior portion of the chest, with radiation to the shoulder. A friction rub developed over this area in the chest. The prothrombin time after anticoagulant therapy was elevated to 50 seconds. The stools showed a ++++ guaiac reaction. On the seventh hospital day the patient again developed severe pain in the right calf and showed a positive Homans's sign on that side. On the ninth day a bilateral superficial femoral-vein ligation was done under local anesthesia. No thrombi were seen in the vessels. A chest film now showed linear shadows of increased density in the left costophrenic angle and possibly a small amount of fluid. The patient was placed on penicillin because of the development of a cough, with the production of a large amount of mucoid white sputum, and also the presence of rales at both lung bases. Four weeks after admission there was an exacerbation of an acute phlebitis in the left leg. The leg was painful and swollen and was about 10 cm greater in circumference than the right leg at the popliteal space. These symptoms developed under dicumarol, which

was therefore discontinued and heparin instituted. The white-cell count had risen to 23,400, with 88 per cent neutrophils. Another x-ray film of the chest showed that the left costophrenic shadow had become more linear, and there was also a small area of increased density in the posterior portion of the right lower lobe. In the fifth week pain again developed in the anterior portion of the chest, and a slight, but unmistakable, jaundice appeared. The serum albumin was found to be 2.7 gm per 100 cc, and the alkaline phosphatase was normal. The cephalin-flocculation test was ++++. Much bile was present in all the stools, many of which also showed a ++++ guaiac reaction. The van den Bergh test was 2/3 to 3/3 mg per 100 cc.

An additional history revealed that one month before entry a sharp pain had developed in the right upper quadrant, associated with anorexia, heart burn and a sensation of epigastric pressure. During that period the patient had lost approximately 14 pounds. In the seventh hospital week epigastric tenderness appeared, and a questionable mass was palpable over the area of maximal tenderness, in the left portion of the epigastrium. Bile continued to be present in the urine and the stools. The total protein was 4.2 gm per 100 cc, and the van den Bergh was 15/5 to 21/2 mg per 100 cc. The mass in the epigastrium was thought to have enlarged, but because of the marked obesity of the patient it could not be well outlined. Throughout the latter part of the patient's course the legs had become markedly swollen and edematous. She weighed 270 pounds terminally, and the edema had extended well up into the back. On the sixtieth hospital day, the patient became restless and hyperexcitable, the respirations slowed, and she died.

#### DIFFERENTIAL DIAGNOSIS

DR. REED A. HARWOOD: May we see the x-ray films?

DR. STANLEY M. WYMAN: This is the film taken on admission. It shows no definite evidence of intrinsic pulmonary disease. The right leaf of the diaphragm is higher than the left—higher than one would expect. The heart shadow is not unusual for a patient of this type. The second set of films, taken ten days later, shows the right leaf of the diaphragm even higher. The films were taken in the supine position, however. There is some indefinite density in the left costophrenic angle, and I believe that there is some fluid in the left pleural cavity. In the lateral film there is a suggestion that the right cavity also has a small amount of fluid in the posterior costophrenic sinus. Eight days later the film still shows indefinite linear density in the left costophrenic angle. It has become smaller, however, and there is some linear density in the right middle lung field. It seems to lie in the base of the right upper lobe anteriorly, close to the chest wall. There is a suggestion of an indefinite

round shadow posteriorly in one of the costophrenic sinuses—I believe the right. The next examination still shows density in the anterior base of the right upper lobe and the round density in the base probably of the right lower lobe. There is still fluid in the left pleural cavity and possibly in the right. The final film taken one month after this examination shows the right leaf of the diaphragm to have been elevated, considerably more so than on the previous examination. It is the only available film taken at that time. It makes one wonder about something going on beneath the diaphragm.

DR. HARWOOD: Would you say that the x-ray films are consistent with small pulmonary infarcts?

DR. WYMAN: They are consistent with multiple infarcts at the base of the right upper lobe and possibly of the left lower lobe.

DR. HARWOOD: The mention of jaundice is the first intimation that there was anything else present in this patient besides thrombophlebitis and multiple small pulmonary infarcts.

I do not get a very clear picture of what the illness was like after the appearance of jaundice. Obviously, she must have been very sick. Was that last film taken with a portable machine?

DR. WYMAN: Yes, it is a film taken at the bedside about seven weeks after the initial films.

DR. HARWOOD: The patient was probably too sick to have intensive studies such as a gastrointestinal series. There must be something in the record that would give additional information. Perhaps in summarizing the history some of the negative data were not included.

DR. MYLES P. BAKER: The alkaline phosphatase was elevated quite significantly at the first determination when she was mildly jaundiced, the figure was 14 or 17 units per 100 cc. The cephalin-flocculation test was not +++ on the first observation, it was either + or ++, and I believe that the thymol-turbidity tests were negative at first. Perhaps that is of some importance. It is true that the patient was too sick for further x-ray studies. During the period of increasing jaundice she was entirely aware of what was going on and doing her best to meet the doctors' requests, taking carbohydrates and so forth, and never presented the picture of a person in severe liver failure.

DR. HARWOOD: Was she conscious to the last day?

DR. BAKER: Yes.

DR. HARWOOD: This is one of those interesting cases in which the patient comes in for one complaint, and then, under observation, much more serious disease develops from which the patient dies. I tried, for a short while, to connect the complications with the initial complaints and wondered if she could possibly have had thrombophlebitis of the vena cava. I know very little about this condition, but I think that, if she had had a thrombosis of the vena cava that propagated beyond the entrance of the renal veins, she would not have survived such

an insult for more than a few days, so I ruled that out. Then there was the possibility of a thrombosis of the portal vein. The standard textbooks have very little to say about this, but they speak of the classic symptoms of hematemesis, ascites and severe upper abdominal pain — not a word about jaundice. I suppose that it could cause jaundice, but the information we have does not suggest portal thrombosis. For one thing, we do not know whether she had ascites. Perhaps Dr. Baker can give a little help on that. I think the weight gain of 40 pounds is rather sensational in a person who had such a serious disease, and I suspect that she had ascites as well as massive edema.

**DR. BAKER:** The patient had such marked edema over the back, loin and flank that it seemed as if she must have ascites, but the percussion note was resonant well over into the side of the abdomen, and one would have to say that the physical signs were not those of ascites, although it was suspected and some observers thought that it was present.

**DR. HARWOOD:** I am going to guess that she had ascites, but usually in portal thrombosis, the ascites develops rapidly, the taps very often are bloody, and the acute disturbance ordinarily leads quickly to death.

We have to admit that this patient had something wrong with the liver. The evidence of that is the low serum protein found in the fifth week of hospitalization, the positive cephalin-flocculation test and the rising serum bilirubin in the absence of obvious biliary obstruction. The question is, What was the matter with the liver? Did she have cirrhosis of the liver? That is one possibility, with polygonal-cell failure as a cause of the increasing jaundice and death. Dr. Baker has said that she did not present the picture of liver failure. One would expect a different type of death, perhaps a much deeper jaundice, and unconsciousness for several days before death. It seems to me that this diagnosis has been excluded.

Could the patient have had a partial obstruction of the common bile duct, as by stone, or a tumor in the region of the ampulla or in the head of the pancreas? Again, I think not, because at no time did she have clay-colored stools. She could not have developed this degree of obstructive jaundice without clay-colored stools. Obstruction of the common duct from any cause thus seems ruled out.

What are the other possibilities? I suppose that metastatic disease is fairly likely. To go back over

the record, "she developed pain in the neck and back, had a gradual loss of energy, easy fatigability and an increased appetite, and had frequent loose bowel movements associated with an urgent gastrocolic reflex," which suggest to me the possibility of some lesion of the upper gastrointestinal tract, or possibly a lesion in the pancreas.

The onset of carcinoma of the pancreas is apt to be insidious. The history does not quite fit that picture. Pancreatic carcinoma can metastasize to the liver, and I suppose it is possible for a situation to develop in which the metastases are largely in the left lobe, pressing on some of the larger bile ducts of the left lobe, whereas those of the right lobe, being uninvolved, permit the passage of bile.

One thinks of carcinoma of the stomach. Again, it does not fit the picture of the complaints that this woman had for a year before admission. The only thing that might fit is the one symptom of the presence of blood in the stool. She had it nearly every time the stool was examined. A carcinoma of the stomach or possibly somewhere else in the gastrointestinal tract might be the explanation of blood in the stools, and metastases to the liver might be the explanation of the jaundice. I have ruled out carcinoma of the large bowel because of the negative barium enema.

I should mention one final possibility, or rather, still another possibility, because there can be no "final" possibility in a case like this — that is, carcinoma of the gall bladder, the common duct or the ampulla. In all these cases jaundice is an early symptom, and it is usually complete. I think these diagnoses have been excluded because there was bile in the stools.

I have not mentioned primary carcinoma of the liver. This condition is most often found as a complication of cirrhosis of the liver. There is some evidence that this patient had cirrhosis, and it is possible that a primary tumor of the liver was also present. Such a diagnosis does not explain the blood in the stools, but this finding could be explained either by the elevated prothrombin time or by portal hypertension.

Although I am far from sure what this woman had, I am going to make diagnoses of cirrhosis of the liver, with a primary carcinoma of the liver, mostly involving the left lobe, thrombophlebitis of the veins of the lower extremities, possibly of the iliac veins, and multiple pulmonary emboli. I am

going to add a second choice—a carcinoma of the pancreas with metastases to the liver

A PHYSICIAN What is the possibility of liver abscess? The diaphragm was elevated. Perhaps there was some fluid there.

DR HARWOOD I meant to ask about the chart, but I am sure that Dr Baker would have told me if she had had a high temperature.

DR BAKER During the period of active phlebitis, the first week, she had a persistent fever, which subsided later.

DR MAURICE FREMONT-SMITH I want to say a few words about this patient, because I was in charge of her health for ten years up to the time of the last illness, including the beginning of it. Looking back, I realize that something happened that we always try to prevent. I cannot see any way now that it could have been prevented. She was a very high-strung woman, who had a tendency to diarrhea. When I first saw her, ten years ago, she had alternating periods of diarrhea and constipation. This continued off and on during the ten years that I took care of her. The diarrhea was affected by the environment. It stopped entirely after any problem that was puzzling her cleared up. Two years before admission to this hospital I did a rectal examination, and a little material being on the end of the glove, I smeared it on a slide, as I always do, and did a guaiac test, which was +++ Two more specimens of stool were examined, and one was faintly positive and the next negative. On the basis of this blood I insisted that she have a proctoscopy and a barium enema. The proctoscopy was done by Dr Donaldson, who was able to go the full distance of the proctoscope. The mucosa was normal. No injection, ulceration or tumors were seen, except some small hemorrhoids, which were thought sufficiently bulbous and engorged to account for the bleeding. That was approximately a year before entry. Four months later the patient again had a positive guaiac test, and I wrote to her at that time "The chances, of course, are very great that there is nothing wrong except the hemorrhoids. On the other hand, we dare not make this assumption. You should have a barium enema and proctoscopy and so forth." At that time the hemoglobin was normal. Barium enema, a month later, was, as stated in the record, absolutely normal, the colon filling rapidly without constant defects or diverticula.

DR BAKER The picture of this woman's last illness, as far as the jaundice is concerned, was that

she was gradually developing extrahepatic obstruction, judging from the laboratory tests. She had had phlebitis in both legs, and we could not really study her adequately. There was a gradual increase in the evidence of liver-cell damage. We wondered at first about the possibility of common-duct stone, recognizing the impossibility of surgery in the presence of the illness unless faced with absolute necessity. The appearance of tenderness in the epigastrium was important. The epigastric mass became more and more obvious, and was not only tender but also the site of persistent pain. Shortly before she died it became obvious that the liver was huge.

DR HARWOOD In view of the information that Dr Fremont-Smith has added, may I change my diagnosis?

DR TRACY B MALLORY Certainly.

DR HARWOOD I shall put carcinoma of the upper gastrointestinal tract—let us say of the stomach with metastases to the liver—as my first choice, and keep carcinoma of the pancreas as my second choice. Hepatoma now seems very unlikely.

DR EDWARD HAMLIN, JR. The only thing that Dr Harwood has not dwelt on is the rather extraordinary lack of efficacy of the treatment for phlebitis. The patient had adequate therapy by both anticoagulins and despite that developed more phlebitis. The veins were tied off at a time when neither vein showed thrombosis above the level of ligation. One would ordinarily assume that the phlebitis at least would not jump the gap. Despite adequate therapy with dicumarol, the lesion went on and both iliac veins became thrombosed. That is unusual and of some importance.

DR HARWOOD Suggesting a metastatic nodule pressing on the vena cava?

DR HAMLIN Suggesting some deficiency somewhere.

#### CLINICAL DIAGNOSES

Carcinoma of liver, metastatic, primary source undetermined, probably pancreas  
Iliofemoral phlebothrombosis  
Pulmonary infarcts

#### DR HARWOOD'S DIAGNOSES

Carcinoma of stomach  
Metastatic carcinoma of liver  
Thrombophlebitis  
Multiple pulmonary infarctions

## ANATOMICAL DIAGNOSES

*Adenocarcinoma of ascending colon, with metastases to liver*

*Thrombophlebitis of both femoral and iliac veins and of inferior vena cava*

Pulmonary emboli, multiple, with pulmonary infarction

Dependent edema

Ascites, slight

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a series of infarcts in the lung some of which were old and completely scarred, and others in all stages of more recent development down to one quite fresh one that must have occurred only a few days before death.

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DR F DENNETTE ADAMS The tumor itself might account for it.

DR MALLORY There were no actual tumor nodules that could be seen pressing on or obstructing the vena cava.

DR ADAMS I meant that the presence of cancer anywhere in the body more or less tends to facilitate thrombosis.

DR FREMONT-SMITH How large was the tumor in the cecum?

DR MALLORY A small annular lesion at the time of autopsy.

DR HAMLIN To go back to the phlebitis. Despite the fact that the prothrombin time without therapy was elevated and despite the further elevation produced by anticoagulants she went on to thrombosis. I am not aware of any comment in the literature that the presence of an overwhelming malignant lesion will produce phlebitis, but it is certainly the impression of people like Dr Allen that such lesions cause phlebitis. The very fact that this rather paradoxical situation took place indicates that an overwhelming malignant tumor was present.

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## BRITISH MEDICINE AT THE CROSSROADS

THE National Health Service Bill of Great Britain was enacted by Parliament on November 6, 1946, and unless changed by Parliament will become effective on July 5, 1948. It will take British medicine a long mile down the left-hand road—in company with the rest of Britain's institutions.

According to this act the Minister of Health is made responsible for setting up a service that is intended to improve the "physical and mental health of the people of England and Wales, and the prevention, diagnosis, and treatment of illness, and for that purpose to provide or secure the effective provision of services. These services will be rendered free of direct cost to the recipients.

The Ministry of Health is also charged with indirect responsibility for organizing and maintain-

ing "General Medical Services, Health Centers, and all other health services, such as Maternal and Infant Welfare, Home Nursing and Midwifery." All doctors may join the new services, none are required to. Remuneration is settled by regulation and is made up of a "fixed part-salary" and a capitation fee, the latter decreasing as the number of a doctor's patients rises. The sale of practices, long an accepted transaction in Great Britain, is prohibited.

The opponents of the act point out that it means centralization of authority in the office of the Minister of Health (and England has had five Ministers of Health in seven years), intervention of a social worker between doctor and patient, the promise to its beneficiaries of complete medical, dental and nursing services without obvious cost, and the creation of a great lay bureaucracy to administer the program. It means also an estimated cost of at least \$1,800,000,000 during 1948 and, inferentially, the ultimate enslavement of all physicians, dentists and nurses into salaried government positions.

A year ago the British Medical Association, as conservative as cold roast beef was once considered to be, held a plebiscite on the act and voted 23,110 against it and 18,972 in favor, with 14,589 members abstaining. On January 31, 1948, a second plebiscite was held that resulted in a vote of 40,814 against the act, or 89.5 per cent of those voting, and 4,735 in favor of it. Another year of socialism, combined with an unfortunately dictatorial attitude on the part of Aneurin Bevan, the present minister of health, has served to crystallize the opinion of British doctors.

It is difficult to know how much of this stiffened resistance is due to an awakened appreciation on the part of the British Medical Association of what the profession stands to lose when the act goes into effect, and how much it may be the result of Mr. Bevan's apparently unco-operative and dictatorial attitude. From the debates that have taken place on the act one is forced to the conclusion that Mr. Bevan's methods have been coercive and his attitude impolitic even to the point where his judgment seems at times to be under the domination of his emotions. Win, lose or draw in this contest, it would seem that the medical profession of Great

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policies of the Commonwealth' On December 3, 1947, a report was made signed by R H Lee, G W Dean, F C Harrington and J D Rivest of the General Court and H D Chadwick, M D, C M Hilliard and L J Smith, M D Dr C F Wilmsky served as consultant, and Drs Carl E Buck and Robert E Rothermel, of the American Public Health Association, were technical advisers Owing to a very short working period and limited budget the commission confined its studies to a few important problems and has asked that it be revived to permit further study A major set of recommendations involves simplifying the pattern of the Massachusetts Department of Public Health to give the Commissioner a modern working organization

The local health units of Massachusetts are the subject of other important recommendations A quotation from the very interesting report of the commission outlines its opinion on local health administration as follows

Massachusetts may take pride in the fact that on the record of its vital statistics as relating to infant mortality maternal mortality the absence of smallpox from the Commonwealth the low typhoid fever morbidity the provision it makes for hospitalizing tuberculosis patients and many other responsibilities it compares favorably with other parts of the country However the Commission is not satisfied with just doing a good job — it wants to see the best possible public health program continue to evolve in Massachusetts That it is not accomplishing all that it might is reflected in tables presented in the appendix in Dr Buck's report which reveals that in the five year period 1941-1945, there were 1,583 deaths from what he calls preventable causes and over 70,000 from controllable causes On the basis that preventable diseases are preventable and that those listed as controllable could be reduced by one half to one third he estimates that 6,126 lives could be saved annually representing if we choose to evaluate lives in terms of \$5,000 each an annual saving of \$30,630,000

The expenditure of a relatively small amount of money for the development of local health departments would to a large extent bring about substantial savings of both lives and money Experiences in Massachusetts and throughout the nation have convinced the Commission that a definite program for the formation of local health departments must be developed including legislation providing for their formation their financial support and their establishment at as early a date as practicable.

The commission has not yet recommended the detailed pattern best adapted for development of local health services in the Commonwealth It has stated, however, that the greatest needs in the formation of local health departments are the following

a sound, state-wide program of education and health information to bring about universal understanding of the need and value of full-time health services, a plan for state financial assistance in the maintenance of full-time local health departments, and an adequate staff of full-time, well trained public-health personnel with good salaries provided to attract such people

It is essential that these important suggestions lead to definite action A very specific recommendation is that the Governor immediately appoint a strong committee to begin the proposed program of health education

The plan for developing full-time local health services for the whole population is, of course, in accord with principles endorsed by the American Medical Association as one deserving the full support of state and local medical societies

### THE GIRLS' TERM

A BILL recently introduced in the New York State Legislature will, if passed, revolutionize and vastly improve the court method of handling cases involving wayward girls, according to a release of the New York Tuberculosis and Health Association Any attempt at solving this problem, which is acute in all metropolitan areas, will be watched with interest and hope The proposed bill has the support of many welfare agencies

The bill has resulted from the obvious need of a specialized court for the girl of sixteen to twenty-one years, as demonstrated by ten years' experience with New York City's Wayward Minor Court for Girls This experience has led students of the problem to believe that not minor repairs but a thorough overhauling of present laws is necessary

A new court to be known as The Girls' Term is proposed The proceedings of this court will be interpreted as civil in character and outside the Code of Criminal Procedure or the Penal Law The court will have the power to order that action be taken to correct a situation within its purview, but the penalty for noncompliance will be a ruling of contempt rather than prosecution under a penal statute and in a different court

Under existing law, parents, who often cause the conditions that are responsible for a girl's way-



wardness, must appear as complainants against their daughter. A situation is thus created that contributes to parent-child hostility rather than to an improvement of these relations. Under the new bill action could be taken on a petition by any responsible person, after the court had made a preliminary investigation. Informal hearings could then be held without the formality of placing girls below eighteen years of age under oath.

Present law requires a police officer who observes a girl conducting herself in a wayward manner to obtain a warrant for her arrest. The proposed law would permit her to be placed in protective custody. Most important of all, the new law, if enacted, provides that an "order of disposition" only need be rendered, and the presiding justice is permitted wide discretion in fixing the terms of such an order.

Gradually, we are breaking away from a puritanical concept of criminality. We are learning that justice may be served better by a helping hand upward than a push with the foot downward. Wayward behavior on the part of any of us may be an expression of insecurity, it should not be treated as a sign of viciousness.

## OBITUARY

### REID HUNT

1870-1948

Reid Hunt, emeritus professor of pharmacology at Harvard Medical School, died on March 7, 1948, after a long illness. He was the last of the great group of medical scientists that established Boston as an international medical center in the first three decades of the twentieth century.

Dr. Hunt was born in Martinsville, Ohio, on April 20, 1870. He received his education there and at Wilmington College and Ohio University, later receiving his baccalaureate degree from Johns Hopkins in 1891. In 1892 he worked with Binz and Nussbaum in Germany, he then returned to Johns Hopkins, where he received his doctorate in physiology in 1896, simultaneously acquiring his degree in medicine from the University of Maryland School of Medicine. From 1896 to 1898 he served as tutor in physiology at Columbia University College of Physicians and Surgeons. The next two years were spent in Egypt on biologic researches. He then returned to Hopkins and began his work in pharmacology under Abel. From 1902 to 1904 he worked in Ehrlich's laboratory in Frankfurt. In 1904 he returned to take the position of chief of

the Pharmacological Division in the Hygienic Laboratory of the United States Public Health Service. Here he remained until he came to the Harvard Medical School in 1913 as professor of pharmacology, becoming emeritus professor in 1936.

Few scientists have left as many permanent contributions. His work was planned with meticulous care and carried out with superb operative technique. As a result of this careful attention to all phases of the problem he was investigating his papers are conclusive and complete. His first paper on the accelerator nerves of the heart is a classic. He demonstrated the balance between the parasympathetic and sympathetic nerves in this organ and explained the mechanism of the nervous control of the heart beat. His second major contribution was a study of the toxicity of methyl and ethyl alcohols. Undertaken long before the prohibition era these studies were the basis of important medicolegal decisions during that unhappy period. To the other important landmarks in pharmacology and physiology that were attained through his researches may be added his work on arsphenamine in which he devised a practical method for predicting the toxicity of samples of this drug and enabled the Commonwealth to distribute it without fear of the dreaded reactions that were common in earlier samples.

In addition to his primary interest in the science of pharmacology he had ever in mind the application of scientific principles to the use of drugs in the clinic. He steadily insisted that physicians prescribe drugs by their official or semiofficial names in preference to the use of proprietary names. In this campaign he led the Council on Pharmacy and Chemistry of the American Medical Association and did much to co-ordinate its reports in *New and Nonofficial Remedies* with the decennial revisions of the *United States Pharmacopoeia*. He was president of the Pharmacopoeial Convention from 1920 to 1930. As a member of the editorial board of the *Journal* he gave freely of his time and sage advice. From his arrival in Boston he was a familiar figure at all the local medical and scientific meetings, and his encyclopedic knowledge of the literature enabled him to contribute much to the success of the discussions that are such a valuable part of such gatherings.

Personally Dr. Hunt was shy and retiring. He was at his best in conversation with individuals and small groups. He had the faculty of thinking through any problem with such thoroughness that when he spoke in council there was nothing left to be said, because of this faculty his advice was widely sought, and he occupied consulting posts of great variety. Through his conversation there ran a vein of humor and kindness and a complete absence of bitterness, though his scientific standards were uncompromising. He had a delightful sense of the ridiculous, his conversation abounded in anecdotes of the great and near-great. He especially loved to

tell of Ehrlich and his absent-mindedness. Above all he possessed great charm and captivated all who had the privilege of being with him intimately.

Many honors came to Dr. Hunt membership in learned societies here and abroad, including the National Academy of Sciences, the American Academy of Arts and Sciences, the Association of American Physicians, the Leopold-Carol Akademie, the Deutsche Pharmakologie Gesellschaft, the American Physiological Society and the American Society for Pharmacology and Experimental Therapeutics. Of the last he was the first secretary and the third president. He was chairman of the Northeastern Section of the American Chemical Society and consultant to the Massachusetts Board of Health and to the Chemical Warfare Service of the United States Army. He was a member of the Drug Standardization Committee of the League of Nations and chairman of the Council on Pharmacy and Chemistry of the American Medical Association.

Dr. Hunt's death removes one of the very last of the group of scientists that raised the United States to a position of eminence in the field of physiology. He in common with his colleagues had a broad biological background to bring to the medical sciences. This gave their researches a fundamental quality that transcended the limits of medical practice. In addition to this background Hunt brought to every discussion his encyclopedic knowledge of the literature including not only his own field but also those of general biology, chemistry and even clinical medicine. The memory he leaves in the hearts of those who knew him intimately is sweet, and his scientific contributions will be a lasting monument.

G P G

## MASSACHUSETTS MEDICAL SOCIETY

### DEATH

Born — Melville G. Boyd M.D. of Dalton died recently. He was in his fifth year.

Dr. Boyd received his degree from Queen's University Faculty of Medicine Kingston Ontario in 1929.

## MISCELLANY

### VETERANS ADMINISTRATION RESIDENCY TRAINING IN NEUROPSYCHIATRY

A limited number of openings are available for July 1, 1948, appointment to the Veterans Administration residency training program in neuropsychiatry. This program is under the jurisdiction of the deans of the Boston medical schools (Harvard, Tufts and Boston University). Training in this program which may be from one to three years is given at Cushing Veterans Administration Hospital, Framingham, Massachusetts; Bedford Veterans Administration Hospital, Bedford, Massachusetts; The Mental Hygiene Clinic of Boston Regional Office of Veterans Administration, Boston; Veterans Administration Hospital, West Roxbury, Massachusetts; and Veterans Administration Hospital, White River Junction, Vermont.

Emphasis to the entire program is on psychiatry with dynamic orientation and includes closed ward, open ward, outpatient and child psychiatry and ophthalmology.

Further information may be obtained from the Chief Neuropsychiatrist, Veterans Administration Branch Office No. 1, 55 Tremont Street, Boston 8, Massachusetts.

## CORRESPONDENCE

### A TIMELY WARNING

To the Editor: The trustees of the Tewksbury State Hospital and Infirmary are much disturbed at the number of patients sent to the Hospital who live only twenty-four or forty-eight hours after entrance. We realize fully that it is difficult to evaluate the condition of many patients suffering from a long chronic disease, and also that removal to the hospital may be justifiable because of economic conditions, even though the patient's condition is serious.

We are writing this letter to call the attention of physicians to the General Laws of the Commonwealth Chapter 122, Sections 16 and 17 which state that no town officer shall remove a sick person to the hospital unless there is reasonable cause to believe that such removal will not injure or endanger his health and in case of doubt shall obtain a certificate of a competent physician that he has examined the patient and that he can be removed without injury to his health.

Recently a decision was handed down by the Massachusetts Supreme Court affirming a judgment of \$7000 against a physician for sending to the hospital, some eighty miles by automobile, a patient who died within twenty-four hours.

Last month a patient was sent from a town some twenty miles from Tewksbury and was found dead on arrival.

We hope that physicians sending patients to Tewksbury will in the future be more careful in their examination of such patients.

ROBERT L. DeNORMANDIE, M.D., Chairman  
Board of Trustees

Commonwealth of Massachusetts  
Department of Public Welfare  
Tewksbury State Hospital and Infirmary

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Studies from The Rockefeller Institute for Medical Research.* Reprints Volume 134, 4<sup>th</sup> paper 605 pp. New York: The Rockefeller Institute for Medical Research, 1947. \$2.00.

This volume of studies brings together in one volume the contributions of members of the staff of the Rockefeller Institute scattered throughout many periodicals. The period covered is approximately the first half of 1947.

*Health Instruction Yearbook 1947.* Compiled by Oliver E. Byrd, Ed. D. M.D., professor of health education and director, Department of Hygiene School of Education, Stanford University. With a foreword by Clair E. Turner, Sc.D., Dr. P.H. National Foundation for Infantile Paralysis. 8<sup>th</sup> cloth 325 pp. Stanford, California: Stanford University Press, 1947. \$3.00.

This basic reference serial, now in its fifth year, abstracts the recent literature on public health. For this volume 323 articles were selected from a total of 1672 read by the editor in 95 different periodicals. The material is divided into twenty-one subject fields. A bibliography of the selected articles is appended to the text. An alphabetical list of sources and a good index conclude the volume. The type, printing and paper are excellent. The volume is recommended for all medical and general libraries and should prove valuable to all persons interested in public health.

*Congenital Malformations: A study of parental characteristics with special reference to the reproductive process.* By Douglas P. Murphy, M.D., assistant professor of obstetrics and gynecology and research associate in the Gynecological Institute of Gynecologic Research, University of Pennsylvania. Second edition. 8<sup>th</sup> cloth 127 pp. with 65 illustrations. Philadelphia: J. B. Lippincott Company, 1947. \$5.00.

This second edition of a monograph first published in 1940 has been expanded by the addition of a second part on the environmental basis of congenital malformations, comprising a study of a series of cases of maternal pelvic irra-

diation and maternal rubella. The first part, from the first edition, discusses the genetic basis in its various aspects. The author concludes from his studies that human congenital defects usually arise from factors present in the male or female germ cells prior to fertilization, and that after fertilization has taken place, they may be produced either by the action of therapeutic amounts of maternal pelvic radium or roentgen irradiation or by a maternal attack of rubella during pregnancy. Likewise, there is no clinical evidence that irradiation of the human egg cell, prior to fertilization, influences the health or development of the resulting infant, and there is only suggestive evidence that an attack of maternal rubella, prior to conception, influences the development of any following offspring. The existing evidence warrants two statements: when a congenital malformation has a genetic basis, there is a greatly increased chance that subsequent brothers or sisters will also be malformed, and when a congenital defect is due to factors that are not genetic in origin, offspring conceived subsequently should be congenitally malformed only with the same frequency as that commonly observed in the population at large. A selected bibliography and index conclude the volume. The publishing is good. This statistical study should be in all reference medical libraries.

*A Text-Book of Pathology. An introduction to medicine.* By William Boyd, M.D., Dipl. Psych., M.R.C.P. Edin., F.R.C.P. Lond., LL.D. Sask., M.D. Oslo, F.R.S.C., professor of pathology and bacteriology of the University of Toronto. Fifth edition, thoroughly revised 8°, cloth, 1049 pp., with 500 illustrations and 30 colored plates. Philadelphia: Lea and Febiger, 1947. \$10.00.

This standard textbook has been revised to date, and much new material incorporated in the text. Sections have been added on stasis, botryomycosis, Tsutsugamushi fever, dermatofibroma, sclerosing hemangioma, hypertensive heart disease, cardiac infarction without coronary occlusion, temporal arteritis, mucosal respiratory syndrome, Löfner's pneumonia, giant-cell pneumonia, chronic disseminated tuberculosis, aspergillosis, intestinal lipodystrophy, alloxan diabetes, renal anoxia, malakoplakia of the bladder, interstitial-cell tumor of the testis, primary splenic neutropenia, pyridoxin-deficiency anemia, the anemia of infections, fibrous dysplasia of bone, hyperostosis frontalis interna, odontogenic tumors, the relation of vitamin C to bone repair and other subjects. The sections on carcinogenesis in relation to enzymes and viruses, silicosis and anthracosis, neurosis and cirrhosis of the liver, Cushing's syndrome, the Rh factor in congenital hemolytic disease, ankylosing spondylitis and Volkmann's contracture have been rewritten. The chapter on allergy, omitted from the previous edition, has been rewritten and restored in this edition. The volume is well published and should be in all medical-reference collections.

## NOTICES

### ANNOUNCEMENTS

Dr. Charles Isenstein announces the removal of his office to 1587 Massachusetts Avenue, Cambridge, for the practice of ophthalmology.

Dr. David E. Kopans announces the removal of his office to 475 Commonwealth Avenue, Boston, for the practice of obstetrics and gynecology.

Dr. Edward T. Moses announces the removal of his office to 543A Highland Avenue, Malden (48).

### NEW ENGLAND OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The spring meeting of the New England Obstetrical and Gynecological Society will be held at Hartford, Connecticut, on Wednesday, May 5, with clinics at the Hartford and St. Francis hospitals and a dinner at the Hartford Club.

### AMERICAN ORTHOPAEDIC ASSOCIATION

A meeting of the American Orthopaedic Association will be held at the Chateau Frontenac, Quebec, from June 3 to 6. This will be a joint meeting with the British Orthopaedic Association and the newly formed Canadian Orthopaedic Association.

### AMERICAN PSYCHIATRIC ASSOCIATION

The 104th annual meeting of the American Psychiatric Association will be held at the Statler Hotel, Washington, D. C., from May 17-20 (the permanent head office of the Association is at 9 Rockefeller Plaza, New York 20, New York), and not in Portland, Oregon, from May 9 to 14, as announced in the April 1 issue of the *Journal*.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 29

##### FRIDAY, APRIL 30

\*9 00-10 00 a. m. Medical Experiences in Germany (March, 1948), Dr. Alexander Marble. Joseph H. Pratt Diagnostic Hospital.

\*10 00 a. m.-12 00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

##### TUESDAY, MAY 4

\*12 00 m. X-ray Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

\*12 15-1 15 p. m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

\*1 30-2 30 p. m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

##### WEDNESDAY, MAY 5

\*12 00 m. Grand Rounds and Clinicopathological Conference. (Children's Hospital) Amphitheater. Peter Bent Brigham Hospital.

\*2 00-3 00 p. m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

\*Open to the medical profession.

APRIL 23 and 24. American Society of Anesthesiologists, Inc. Page 582, issue of April 15.

APRIL 26. New England Heart Association. Page 582, issue of April 15.

APRIL 26-29. American Dermatological Association. Page 456, issue of March 25.

APRIL 28. Massachusetts Society for Social Hygiene. Page 582, issue of April 15.

APRIL 29-MAY 2. American Academy of Pediatrics. Page 240, issue of February 12.

APRIL 30 and MAY 1. American Gastro-Enterological Association. Page 456, issue of March 25.

MAY 1. Suffolk District Medical Society. Page 543, issue of April 8.

MAY 3. American Society for Clinical Investigation. Page 456, issue of March 25.

MAY 3 and 4. Association of American Physicians. Page 492, issue of April 1.

MAY 4. Suffolk District Medical Society. Annual Meeting. Page 582, issue of April 15.

MAY 4 and 5. Association of Military Surgeons of the United States. Page 456, issue of March 25.

MAY 5. New England Obstetrical and Gynecological Society. Notice above.

MAY 6. Suffolk Censors' Meeting. Page 344, issue of March 4.

MAY 6-8. American Association for the Study of Gonorrhea. Page xiii, issue of July 31.

MAY 11. Harvard Medical Society. Amphitheater of Building D, Harvard Medical School. 8:00 p. m.

MAY 12-14. American Association of Genito-Urinary Surgeons. Skytop Lodge, Skytop, Pennsylvania.

MAY 13. Indications for the Use of Forceps. Dr. Roy J. Heffernan, Pentucket Association of Physicians. 8:30 p. m. Haverhill.

MAY 16-22. American Board of Obstetrics and Gynecology, Inc. Page 344, issue of March 4.

MAY 16-23. International College of Surgeons. Page 136, issue of January 22.

MAY 17-19. American Ophthalmological Society. Page 492, issue of April 1.

MAY 17-20. American Urological Association. Hotel Statler, Boston.

MAY 17-20. Association for the Study of Internal Secretions. Page 492, issue of April 1.

MAY 17-20. American Psychiatric Association. Notice above.

MAY 18-22. American Association on Mental Deficiency. Copley Plaza Hotel, Boston.

MAY 20-25. American Board of Ophthalmology. Page 170, issue of January 29.

(Notices concluded on page xv)

**NOTICES (Concluded from page 614)**

- MAY 23-28.** American Physiotherapy Association Page 543 Issue of April 8  
**MAY 24-26.** American Gynecological Society Page 543 Issue of April 8  
**MAY 25-27.** Massachusetts Medical Society Annual Meeting Hotel Statler Boston  
**MAY 27-29.** American Surgical Association Page 455 Issue of March 25  
**JUNE 3-6.** American Orthopaedic Association Page 614  
**JUNE 7-10.** National Gastroenterological Association. Page 455 Issue of March 25  
**JUNE 14-16.** American Neurological Association Page 582 Issue of April 15  
**JUNE 17-20.** American College of Chest Physicians. Page 455 Issue of March 25  
**JUNE 20 and 21.** American Radium Society Page 543 Issue of April 8  
**JUNE 21 and 22.** American Society for the Study of Sterility Page 384 Issue of March 11  
**JUNE 25 and 26.** Christian Medical Society Page 492 Issue of April 1  
**JUNE 28-30.** American Academy of Pediatrics Hotel Schroeder Milwaukee Wisconsin  
**JULY 6-24.** Students International Clinical Congress. Page 455 Issue of March 25  
**JULY 12-17.** First International Poliomyelitis Conference Page 36, Issue of January 1  
**AUGUST 11-21.** International Congress on Mental Health. Page 544 Issue of March 4  
**AUGUST 23-26.** International Society of Hematology Page 419 Issue of March 18  
**AUGUST 26-28.** American Association of Blood Banks. Page 420 Issue of March 18  
**SEPTEMBER 7-11.** American Congress of Physical Medicine Page 582 Issue of April 15  
**SEPTEMBER 13-15.** American Academy of Pediatrics Olympic Hotel Seattle Washington  
**SEPTEMBER 20-23.** American Hospital Association Page 310 Issue of February 26  
**SEPTEMBER 29.** Mississippi Valley Medical Editors Association Page 170 Issue of January 29  
**OCTOBER 6-9.** American Board of Ophthalmology Page 170 Issue of January 29  
**NOVEMBER 1-3.** American Clinical and Climatological Association Page 584, Issue of April 15  
**NOVEMBER 8-12.** American Public Health Association Page 420 Issue of March 18  
**NOVEMBER 20-25.** American Academy of Pediatrics. Annual Meeting Chalfonte-Haddon Hall Hotel, Atlantic City New Jersey  
**DECEMBER 7-9.** Southern Surgical Association Annual Meeting Page 543 Issue of April 8

**DISTRICT MEDICAL SOCIETIES**

- FRANKLIN**  
**MAY 11.** Annual Meeting Hotel Walden Greenfield.  
**MIDDLESEX EAST**  
**MAY 12.** Annual Meeting 6:45 p.m. Bear Hill Golf Club, Wakefield.  
**PLYMOUTH**  
**MAY 20.** Lakeville Sanatorium Lakeville  
**SUFFOLK**  
**MAY 1.** Spring Dinner  
**MAY 4.** Annual Meeting  
**MAY 6.** Censors Meeting  
**WORCESTER**  
**MAY 12.** Annual Meeting

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## AN EVALUATION OF CURARE IN SPASTICITY DUE TO SPINAL-CORD INJURIES\*

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FRAMINGHAM, MASSACHUSETTS

IN 1850 Claude Bernard<sup>1</sup> demonstrated the site of action of curare to be the neuromuscular junction. His experiments have been verified by numerous investigators, and in 1935 West<sup>2</sup> and King<sup>3</sup> clarified the mode of action and enumerated the pharmacologic properties of the drug. It was not until 1943 that Wintersteiner and Dutcher<sup>4</sup> crystallized the quaternary ammonium salt, d-tubocurarine chloride. Recent availability of this pure preparation has stimulated clinical and pharmacologic investigations.

The gross effects of curare on the normal human subject have been thoroughly investigated. The intrinsic musculature of the toes and eyes demonstrates early paresis, which successively involves the muscles of the limbs, head and neck. Inter-costal muscle relaxation is soon followed by paralysis of the diaphragm. During the early stages of curarization, the patient complains of blurring and fuzziness of vision. The eyelids droop, diplopia develops, and the jaws relax. There is weakness and heaviness of the neck muscles progressing to head drop. Further administration of the drug produces complete peripheral paralysis and, finally, respiratory arrest.<sup>5</sup> These signs and symptoms disappear in reverse order, and the rate of disappearance is dependent upon the nature of the curare preparation administered.

Although it is known that curare exerts its influence primarily at the myoneural junction, the exact mode of action remains in doubt. Eccles, Katz, and Kuffler<sup>6-10</sup> demonstrated that the end-plate potential in fully curarized muscle rises to sub-threshold levels and subsides without initiating muscle response. The size of the potential—that is, the degree of depolarization—depends in part on the concentration of the curare in the muscle. The degree of block is controllable, and certain frequencies can be suppressed. This action may well explain obliteration of various involuntary move-

ments while normal voluntary contractions continue.<sup>11</sup>

Clinically, curare has been used with value in a number of conditions necessitating muscle relaxation. Curare therapy of tetanus has met with some success,<sup>12-18</sup> and convulsions incident to shock therapy are effectively diminished.<sup>16-18</sup> However, it is in anesthesiology that this drug has achieved its maximal usefulness to date. In 1942, Griffith<sup>19</sup> reported the use of curare as an adjuvant to general anesthesia, and numerous excellent studies in succeeding years have thoroughly established its value in this field.<sup>20-25</sup>

In 1942 Denhoff and Bradley<sup>26</sup> conducted a controlled study of the effectiveness of aqueous curare in relieving the spasms of children with cerebral diplegia. They concluded that progress under physical therapy was definitely accelerated in these subjects. Muscular relaxation with maximal therapeutic dosages was maintained for a period of approximately four days. Burman,<sup>27</sup> Bennett<sup>28</sup> and Schlesinger<sup>11</sup> reported similar success in patients exhibiting spasticity and rigidity.

Recent reports have indicated that curare might offer valuable aid in the amelioration of spastic paraplegia and paraparesis.<sup>11, 29, 30</sup> Schlesinger<sup>31</sup> administered aqueous curare to 11 patients with extreme spasticity due to spinal-cord injuries and obtained excellent but transient relaxation. A suspension of d-tubocurarine chloride in a peanut-oil and white-wax mixture was prepared in an effort to retard the rate of absorption. The curare effect was found to be prolonged up to three days in some cases, and effective reduction of spasticity<sup>32</sup> was not accompanied in any case by unpleasant side reactions. The effect of the curare in oil on patients exhibiting voluntary function masked by spasm seemed more dramatic than that observed in paraplegic patients.

Severe spasm of muscle groups innervated below the level of the cord lesion is frequently a major manifestation of spinal-cord injury, whether due

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†The views expressed in this article are those of the authors and do not necessarily represent those of the Veterans Administration.

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Assistant resident, a neurology, Montefiore Hospital, New York City; formerly research fellow in neuropathology, Neurological Unit, Boston City Hospital.

Spasticity, and elsewhere in this article the term "spasticity" refers to the involuntary muscular contractions occurring in spastic muscle groups innervated below the level of the cord lesion. More detailed descriptions of these movements are given in the case reports presented below.

to trauma or to an infectious or neoplastic process Spasm may be said to be related more or less intimately to the numerous complications following

are certainly exacerbated by flexion spasms of the lower extremities, and in many cases the continual friction is a major etiologic factor Prolonged spas-

TABLE 1 *Data in Patients with Injuries of Spinal Cord*

PATIENT	LEVEL OF LESION	DEGREE OF TRANSECTION	INTERVAL SINCE INJURY	DURATION OF SPASMS	TYPE OF SPASM
			days	days	
Patients given d-tubocurarine					
H B	2nd dorsal segment	Complete*	805	763	Adductor flexor, alternating with generalized extensor
E H	6th dorsal segment	Partial	740	689	Abductor-flexor, with abdominal and gluteal
D K.	4th dorsal segment	Complete*	660	618	Extensor, with moderate adductor-flexor
A K.	3rd dorsal segment	Partial	975	933	Adductor-flexor, with abdominal and gluteal
H K.	6th dorsal segment	Complete†	858	800	Adductor-flexor, with strong abdominal and gluteal
H. E. K.	7th cervical segment	Partial	661	634	Flexor of upper extremities and extensor of lower extremities
D L. R.	5th dorsal segment	Complete*	953	933	Adductor-flexor (80 per cent), extensor with abdominal, gluteal (20 per cent)
W M.	2nd dorsal segment	Complete*	902	857	Flexor and extensor with abdominal and gluteal
R. Mc.	4th dorsal segment	Complete*	950	715	Adductor-flexor, with abdominal and gluteal
R. N.	5th dorsal segment	Complete*	211	169	Severe adductor-flexor, with mild generalized extensor
A. N.	6th dorsal segment	Partial	706	692	Severe adductor-flexor, with moderate generalized extensor
F N.	3rd dorsal segment	Complete*	620	590	Alternate adductor flexor with extensor, abdominal and gluteal
P P.	5th dorsal segment	Complete*	749	719	Strong extensor, with moderate adductor-flexor
J S.	5th cervical segment	Partial	759	719	Adductor-flexor, with abdominal and gluteal
L. S.	10th dorsal segment	Complete*	353	323	Adductor-flexor, with abdominal and gluteal
M E S.	6th dorsal segment	Partial	1071	981	Approximately equal adductor-flexor and extensor
R. S.	9th dorsal segment	Partial	494	359	Moderate adductor-flexor, with mild extensor and abdominal and gluteal
Patients given physiologic saline solution					
R. B.	7th cervical segment	Complete†	232	205	Torsion of trunk and shoulders, mild knee-flexor
J C.	3rd dorsal segment	Complete*	777	734	Adductor-flexor, with extensor, abdominal and gluteal
F C.	5th dorsal segment	Partial	623	593	Adductor-flexor (90 per cent), mild abdominal and gluteal
J D.	8th dorsal segment	Complete*	610	568	Adductor-flexor, with abdominal and gluteal
J Dr.	4th dorsal segment	Complete*	844	814	Adductor-flexor (80 per cent), with mild extensor
L. D.	9th dorsal segment	Complete*	788	604	Dominant adductor-flexor, with mild abdominal and gluteal
H F.	7th dorsal segment	Complete*	629	610	Severe adductor-flexor, with minimal extensor
T F Mc.	5th dorsal segment	Complete*	850	775	Adductor-flexor, with abdominal and gluteal
J M.	7th dorsal segment	Complete†	668	620	Adductor-flexor, with abdominal and gluteal
W Mc.	9th dorsal segment	Complete*	800	780	Adductor-flexor, with moderate extensor
R M.	5th dorsal segment	Complete*	820	790	Adductor-flexor, with abdominal and gluteal
D P.	5th dorsal segment	Complete*	742	712	Abdominal and gluteal, with flexor-adductor
R P.	5th dorsal segment	Complete*	741	729	Alternate extensor and adductor flexor
R. St.	2nd dorsal segment	Complete*	751	709	Abdominal, with plantar flexor of feet
M S.	6th dorsal segment	Partial	998	870	Equal, alternate extensor and flexor-adductor
H W.	7th dorsal segment	Complete*	277	155	Adductor-flexor, with abdominal and gluteal
J Z.	3rd dorsal segment	Complete*	746	566	Strong extensor, with mild intermittent flexor-adductor

\*Anatomic transection of the spinal cord (verified by exploration)

†Physiologic transection of the spinal cord

such an injury Munro<sup>32</sup> has discussed these complications in detail

Troublesome decubitus ulcers are frequently encountered in patients with cord injuries. These lesions, when present on the heels, knees or hips,

may lead to permanent contractures of tendons and joints, and neither intensive physiotherapy nor surgery is of much avail. Bladder management is difficult to achieve in these subjects, and the important task of teaching the patient to ambulate

effectively is virtually impossible. The person with spasm can be forced into braces, which can be locked in position, but he will never learn the balance that

a wheelchair life. Unfortunately, only a few patients are able to "tire" their minimal spasms with a short period of exercise or physiotherapy.

TABLE 1 (Continued)

DEGREE OF SPASM		DEGREE OF PAIN		REMARKS
BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
+++	+++	0	0	No improvement; dizziness on 9th and 13th days.
++++	+	++	+	Marked improvement; moderate relaxation and drowsiness on 3rd, 5th and 7th days.
++	+	0	0	Questionable improvement; dizziness on 5th, 9th and 21st days.
++++	++++	0	0	Spasms unabated; weakness and diplopia on 5th, 11th, 15th and 17th days.
++++	++++	0	0	Spasms unabated; no symptoms of any type.
++	++	++	++	Spasms unchanged; no symptoms.
+++	++++	+	—	Spasms worse; bitter complaints of visual blurring on 5th, 7th and 9th days.
++	++	+	+	Questionable improvement; headache on 7th and 9th days.
++++	++++	+	+	No symptoms; spasms unabated.
++++	++++	+	+	Severe spasms; nystagmus; slight dizziness on 7th day.
++++	++	++	+	Hamstrings and abdomen moderately relaxed; patient sleeps better.
++++	++++	++	++	Patient seemed suggestible; spasms unchanged.
++	++	0	0	Spasms unchanged; moderate dizziness on 7th, 9th and 11th days.
+++	+++	+++	+++	Weakness, blurring and severe dizziness through out.
+++	+++	+	+	Patient asymptomatic; spasms unchanged.
++++	++++	+	+	Fitting edema of hands and feet on 5th, 7th and 9th day; spasms unchanged.
+++	+++	+	+	Patient asymptomatic, with no change in spasms.
++	++	++	++	No symptoms; spasms unchanged.
+	++	0	0	Spasms worse, with weakness, on 7th, 17th and 19th days; dizziness on 15th day.
+++	++	0	0	Dubious improvement in spasms.
++++	++++	0	0	No changes of any nature noted.
++++	+++	0	0	Spasms generally improved; weakness on 17th and 19th days and diarrhea on 7th day.
+	+	0	0	Questionable relief of spasms; severe weakness on 17th and 19th days; syncope on 5th day.
++++	+	0	0	Spasms markedly alleviated in all components; patient sat for first time.
++++	++++	0	0	No changes of any type noted.
++++	++	0	0	Spasms moderately but definitely decreased; drowsiness on all days.
++	++	0	0	Patient asymptomatic; spasms unabated.
++	++	0	0	Spasms unchanged; but patient sleeps more; drowsiness on 7th, 9th and 11th days.
+++	+++	0	0	Spasms unabated; dizziness on 7th and 9th days.
++	++	0	0	No changes of any type noted.
++	++	0	0	Spasms unchanged; dizziness on 7th and 9th days.
++++	++++	+	+	Excitable patient; spasms unchanged; weakness on 5th, 9th and 17th days.
+	++	+	+	Spasms seemed worse; patient asymptomatic.
+++	+++	+	0	Spasms unchanged; drowsiness on all days, weakness on 3rd, 13th and 15th days.

is essential to walking. Pelvic jackknifing, asymmetry of spasms in the lower extremities and the utter unpredictability of onset militate strongly against satisfactory adjustment. The patient becomes wary, loses confidence and resigns himself to

During the past year, we have attempted to relieve spasm by a number of methods. Prostigmine and atropine administered parenterally have not been successful. Local injection of spinal nerves with procaine or related preparations provides relief of



very short duration. Anterior rhizotomy has been performed as a last resort, the extent of nerve section depending upon the problem presented by the individual patient. Effort has always been made to carry out the simplest, safest and least destructive procedure first, anterior rhizotomy being reserved for patients not benefited by prolonged trial of the less radical methods.

Transient beneficial effects were observed to follow the intramuscular injection of aqueous curare, but were nullified by incapacitating toxic symptoms. It was believed that d-tubocurarine in oil, because of its slow rate of absorption, might provide longer lasting relief of spasms without toxic side reactions. Therefore, the present study was undertaken.

### METHODS

Thirty-four patients on the Paraplegia Service were selected as spastic problems. The spasms ranged from mild muscle-group twitchings of almost subclinical importance to spasticity so marked as to prevent any form of ambulation. Levels of cord injury ranged from the fifth cervical to the tenth thoracic segment. Seventeen patients had been injured by high-explosive shell fragments, and 10 by gunshot wounds, and 7 had sustained compression fractures of one or more vertebrae. Nine men had suffered partial lesions of the cord, and 25 demonstrated clinical evidence of complete transections. In the average patient, spasms were first noted approximately six weeks after injury (Table 1).

The 34 patients were divided into two groups of 17 each, and an attempt was made to distribute them evenly according to the level of injury and severity of spasm. Patients in the first group were given 175 mg (1 cc) of d-tubocurarine in oil and wax\* intramuscularly every forty-eight hours for a total of ten doses. Those in the other group were given physiologic saline solution (1 cc) intramuscularly at similar intervals and for the same period. Two series were studied, separated by an interval of approximately two months. In the first series, 16 patients were given injections, half of them receiving the medication, and half physiologic saline solution. The second series was managed similarly with a total of 18 patients. No attempt was made to isolate those under treatment, and communication between patients of the same and different wards was unrestricted. To minimize prejudicial estimates of improvement because of previous knowledge of the medication received, neither the observer in the first series (R A K) nor that in the second (D S B) was cognizant of the distribution of controls or drug injections. The distribution remained unknown to the observer until all injections had been completed and his written report submitted. In each series, one nurse gave injections

from beginning to end of the treatment period. Patients were told only that they were receiving "medicine for spasms." Nurses and doctors were under strict injunction to guard against elaboration of this single statement. The injections were completely prepared, and the needles attached under sterile conditions in a room separate from the main ward. To promote efficiency, ten or fifteen syringes were carried in a closed container from ward to ward. A hot-water bottle covered with a sterile towel served to maintain the d-tubocurarine in liquid state. All syringes were taped to the 1-cc mark, the quantity of injectable material kept the same in each syringe, and the barrel and needle end covered by the nurse until the moment of injection into the gluteal region. The necessity for such elaborate precautions is demonstrated by reference to the case reports presented below.

Clinical observations by doctors, physiotherapists and nurses and subjective reports by the patients were accorded most weight in evaluation of the results obtained. Clinical estimates were based upon observation of the patients' ability to ambulate and maneuver between bed and wheelchair, response of spastic extremities to pinprick and other stimuli, and resistance of the extremities to passive motion. Each patient was questioned about the frequency, duration, severity and "sensitivity" of spasms during the periods between injections, and special care was taken to avoid leading remarks. Most patients volunteered detailed statements with as little prompting as the question, "How are your spasms?" or "Are you having any trouble?"

### RESULTS

Amelioration of spasms was apparently obtained in 7 of the 34 patients. Three of these patients were receiving curare, and 4 were receiving physiologic saline solution. The degree of estimated improvement varied, but the most marked "relief" occurred in 2 patients in the latter group. In none of the patients was improvement so marked as to justify continued administration of curare. Twenty-seven patients were unimproved, 14 of these having received curare, and 13 having received physiologic saline solution.

Pain was considered to be lessened in 3 patients—2 in the medication group and 1 in the control group. No changes occurred in the remaining 31 patients.

Toxic symptoms were frequent and misleading. Manifestations of such symptoms by patients in the control group were usually indistinguishable from the complaints of patients actually receiving curare and frequently led to incorrect estimates of the type of medication being administered.

The role played by suggestibility in therapy of this type of patient was clearly demonstrated. Intramuscular injection of d-tubocurarine in oil demonstrated no effects on spasticity that could not be

\*The tubocurarine was supplied by E. R. Squibb and Sons, New York City.

duplicated with intramuscular injection of physiologic saline solution

The following case reports are illustrative of the series as a whole

**CASE 1** J. S., a 21-year-old man, was wounded January 20 1945, by a .31-caliber bullet, which entered the left anterior triangle of the neck, emerging through the left posterior triangle. He sustained a compound comminuted fracture of the bodies of the fifth and sixth cervical vertebrae, with complete loss of all motor and sensory modalities below the level of the fifth cervical segment. Within 2 days he was able to flex the left leg, and 7 days after injury he began to regain some motor power in the upper extremities. Depressure sensation returned completely below the level of the second rib. Débridement was performed 9 days after injury, but no attempt was made to visualize the dura or spinal cord. The patient developed a large sacral decubitus ulcer en route to the United States but the neurologic status was gradually improving. Examination in September demonstrated patchy hypesthesia which ended at the fourth lumbar dermatome on the left and the fifth lumbar and first sacral dermatomes on the right, with complete anesthesia below those levels. Motor activity returned to the left upper extremity, the right hips were weak but contracting voluntarily, and there was fair extension and flexion of the thigh on the pelvis and the leg on the thigh in the left lower extremity. Voluntary motion was present in the right lower extremity but to a lesser extent. There was no movement of the feet or toes. Concurrently with the gradual re-establishment of voluntary motor power approximately 2½ months after injury, the patient began to notice adductor flexor muscle spasms. The involuntary movements lasted approximately 30 seconds and were set off by changes in position or by attempts at initiating motion in the lower extremities. Turning in bed particularly excited movements. Abdominal spasms became more and more frequent. Despite daily physiotherapy and prolonged treatment with prostigmine and aqueous curare, flexion contractures of hips, knees and ankles gradually developed. In June, 1946, because of the danger of ankylosis a series of orthopedic procedures was carried out, including bilateral fasciotomy of the hips, bilateral adductor-logous tenotomy, bilateral triple hemisection of the Achilles tendon and left hamstring tenotomy. The lower extremities were placed in casts split over the popliteal space, and the knee flexion was slowly reduced by wedging. At the end of 1 month both lower extremities demonstrated full range of motion but with release from the cast, strong spasms again flexed the right leg. Brace and crutch ambulation began in August, 1946 but the patient continued to be severely hampered by spasms. Attempts by the patient to inhibit flexor spasms voluntarily in the left lower extremity began to evoke strong extensor spasms.

Ten injections of 1 cc (175 mg) of d tubocurarine in oil and wax were administered in the manner described above.

There was no improvement in severity, frequency or sensitivity of spasm. Toxic symptoms of overdosage occurred throughout the entire course of treatment as evidenced by blurring of vision, diplopia, dizziness, headache and weakness. Two episodes of nausea and vomiting occurred within 1 hour of injection.

**CASE 2** F. N., a 30-year-old man was injured on June 9 1945 when the truck in which he was riding plunged off a cliff in Germany. He sustained immediate complete paralysis with a sensory and motor level at the fifth dorsal dermatome. A ray study revealed comminuted fractures of the transverse processes and bodies of the fifth and sixth dorsal vertebrae and lumbar puncture demonstrated partial block. The patient was placed in hyperextension and returned to the United States. Onset of reflex activity was noted 1 week after injury with the appearance of bilateral hallux dorsiflexion. One month later there was mild abdominal spasm, and within the following few weeks mild thigh flexion appeared. At 3 months he developed an extensor component, which appeared while he was lying on the side and back. The adductor flexor type of mass reflex increased gradually in severity, and by March 1946 the spasms were strong usually extensor in pattern and set off by almost any stimulus.

Laminectomy performed on August 14 revealed an atrophic spinal cord with cystic degeneration at the level of the fourth and fifth dorsal vertebrae. Approximately one eighth of the left posterolateral column was stated to be anatomically intact. The posterior roots of the fifth dorsal segment were severed bilaterally in an attempt to relieve the girdle pains. No change resulted except for an increase in pain at that level. Ambulation was first begun on long leg braces with a back brace in April. With the exception of the postoperative laminectomy period the patient subsequently continued to ambulate. Flexion-adduction and extension spasms markedly interfered with walking and the patient had reached a point beyond which he could not progress.

Ten injections of 1 cc (175 mg) of d tubocurarine in oil and wax were administered in the manner described above.

No improvement was observed in the severity, frequency or sensitivity of spasms. Girdle pain remained the same. The patient experienced dizziness on the 5th day of treatment and some blurring of vision on the 21st day.

**CASE 3** J. D., a 34-year-old man was wounded on November 24, 1944 by a high-explosive shell fragment, which struck him in the interscapular region, inflicting a compound comminuted fracture of the laminae and bodies of the third and fourth dorsal vertebrae. There was no loss of consciousness but immediate complete sensory and motor paralysis distal to the third thoracic dermatome. After emergency supportive treatment, débridement was done. The dura was visualized, found to be intact and stated to pulsate well but the cord was completely severed. Involuntary movements began approximately 1 month after injury. They first manifested themselves as mild flexion contractions involving the thighs, legs and feet. The strength and frequency of the spasms gradually became more pronounced and 5 months after injury lumbar abdominal and adductor components entered the flexion picture. In September 1945, extensor thrust began bilaterally and an extensor component, which lasted 20 to 30 seconds, appeared with marked fatigue. To date the patient has continued his efforts at ambulation. Adductor spasm and scissoring have been partially relieved by obturator neurectomy and adductor tenotomies and it was found necessary to perform sections of both Achilles tendons to correct plantar flexion contractures. Progress has been practically nil. Strong triple flexion spasms together with severe extensor spasms have been extremely difficult to cope with. Prolonged trial with intravenous and intramuscular curare, prostigmine and atropine did not benefit the patient and operative relief was repeatedly refused. The neurologic status and general physical condition have remained unchanged for the last ten months.

The patient was included in the control series and given ten injections of physiologic saline solution throughout the prescribed course of treatment.

On the 3rd day of treatment he thought that the extensor component of the spasm was of somewhat shorter duration than normal for him. On the 5th day the same report was given and on the 7th day he reported and demonstrated definite relaxation of flexor, extensor, abdominal and gluteal spasms. He also reported mild diarrhea on that day which he attributed erroneously to the medication being administered. He continued to report daily that the spasm was improving saying "I feel more relaxed all over" and "The spasms don't last as long and I can bend my legs with my hands without making the spasm start—I could never do that before." On the 17th day he complained of mild weakness but no other toxic symptoms. He felt definitely improved and repeatedly requested after completion of the injections that they be resumed.

**CASE 4** L. D., a 29-year-old man, fell 50 feet from a hangar roof on December 21 1945 striking a concrete floor. There was immediate complete motor and sensory loss below the level of the sixth dorsal dermatome. A ray study revealed compression fractures of the bodies of the seventh, eighth and ninth dorsal vertebrae. On the following day exploratory laminectomy demonstrated complete aortic transection of the spinal cord with a gap between the ends, at the level of the ninth dorsal vertebra. There was considerable contusion of the cord at the levels of the seventh and eighth and the posterior roots of the eighth and ninth

dorsal segments were lacerated. Involuntary movements were first noted by the patient approximately 6 months after injury. They began as fibrillary twitchings in the hamstrings and gradually spread to the abdominal and gluteal muscles. A triple-flexion pattern of moderate severity evolved, with occasional abduction spasms of the thighs. He was able to ambulate throughout the summer of 1946 on long leg braces with a back brace. For the past 2 months he has had extension spasms of both thighs on rising from a supine position. Bilateral plantar flexion is a part of this general pattern. The spasms usually last about 5 to 10 seconds, but may occur at any time and are more marked while he is sitting than when he is standing. Ambulation has been only moderately hindered by the involuntary activity. The main problem confronting this patient has been poor bladder control as an accompaniment of the general spasm picture. Tidal drainage was attempted in March, 1947, with no success. The bladder has a small capacity and requires frequent emptying, with no assurance that the patient will remain dry.

This patient was selected for the control series and given 1 cc of physiologic saline solution intramuscularly every 48 hours for the usual injection period.

There was no change on the 3rd day. On the 5th day he noticed diarrhea three or four times, but there was no change in the spasms. On the 7th day he reported definite improvement in spasm frequency and severity, but complained that along with the relaxation he became dizzy, fainted and was unconscious for a period of 2 or 3 minutes. His ambulation instructor held him erect until the period of dizziness passed, but he suffered weakness and dizziness for 5 hours after the injection on that day. On the 9th day of treatment the patient stated that he was improved in all respects, with relaxation of flexor, extensor, abdominal and back spasms. The bladder was not "firing off" so frequently. He maintained this state of improvement throughout the entire course of treatment. On the 13th day he again complained of mild weakness and dizziness. He felt quite definitely that his spasms were improved and stated that they "didn't last so long." There were quite bitter complaints about the toxic symptoms he was manifesting, and because of them he wished to discontinue the injections, but was persuaded to complete the injection course. At the termination of treatment he expressed the opinion that although the spasms had been definitely improved, the fatigue and weakness accompanying injections more than counterbalanced this improvement. Accordingly, he would "rather have the spasms."

## DISCUSSION

In an attempt to evaluate the results of any medical therapy for spasms, certain limitations and difficulties must be emphasized. No objective method of measuring the degree of spasm is entirely satisfactory. Caliper or tape measurements of the range of motion possible in the spastic limb do not yield accurate data. The unpredictable and frequently abrupt "normal" variations in intensity of spasm from hour to hour are extremely confusing. It is very unusual indeed for a patient to reproduce the identical intensity and pattern of spasticity week after week. He may volunteer the information that he has recently been much less spastic than usual, but testing will demonstrate spasms that appear to be of equal or greater severity than those noted during a day when he was, by his own estimate, "jerking all the time." If the time necessary for spasm to "tire" against a given stretch is taken as an index, the same objection holds.

Normal daily variation, which is dependent upon factors not yet explained, serves to minimize the value of such measurements. Myometrograms

demonstrating the action potentials of spasmodically contracting muscles are impractical for the same reason. Standardization preliminary to recording each measurement is extremely difficult, and it is virtually impossible to establish a base line for comparison of one patient with another. Still photographs, as might be expected, are misleading. It was, unfortunately, not possible to obtain moving pictures of the reflex activity in these men. Slow-motion-picture analysis of the reflex movements resulting from a standard stimulus should yield fairly accurate data.

The dosage schedule utilized in this series was arrived at after some deliberation. As with any drug, optimal therapeutic dosage and tolerance vary with each patient. Available studies indicate that a single effective dose will continue to manifest its effect for forty-eight to seventy-two hours<sup>11, 27-29</sup>. In administering 1 cc of d-tubocurarine in oil every forty-eight hours, we preferred to err on the side of overdosage, with the hope that toxic symptoms would not become disabling and that the majority of patients would fall within the therapeutically effective range of the drug.

It must be realized that we were dealing with patients whose injuries had placed them in a unique psychologic situation. A profound sense of inadequacy governed their daily lives. Despite a superficial rationalization encouraged by association with similarly disabled patients, there remained in these men deep feelings of inferiority and helplessness. They had been forced to the logical conclusion that their disability was in all probability a permanent one, and that they would never become normal. But such a realization did not prevent severe conflict with the hope (usually unexpressed) that some new treatment would be found or that some miracle would occur to restore their limbs. Popular articles reporting amelioration or "cures" in almost any disability, vaguely or directly related to spinal-cord injury and its sequelae, brought immediate inquiry and demand for explanation. There was fertile ground for acceptance of ideas that are medically and surgically unsound. Suggestibility was maximal, and if the desire for improvement was of sufficient strength "improvement" would result no matter what agent was employed.

The importance of suggestion is strikingly emphasized by the patients who were given physiologic saline solution (Table 1). The "toxic symptoms" demonstrated by 4 patients are easily attributable to suggestion, but alleviation of spasm, sufficiently marked to impress the observer, demonstrates the facility with which suggestion completely obviates clinical observation. It stresses the need for controlled trial of any new drug in these patients. It is evident that a striking reduction of spasm can be produced by suggestion in certain patients with proved anatomic severance of the spinal cord. The

psychogenic factors involved, and their relation to spasm, are complex and deserve further investigation.

It is apparent that in neither series were the observers able to estimate correctly the patients receiving d-tubocurarine (Table 1). Of the total of 34 patients, the type of injection administered was judged incorrectly in 16. Nine patients receiving curare were estimated to be receiving physiologic saline solution, and 7 of those receiving saline solution were judged to be in the curare group. It is therefore obvious that little or no therapeutic effect attributable to curare was observed.

Twenty of the 34 patients exhibited apparent effects of "overdosage" at one time or another, 11 of these received curare, and 9 received saline solution. Diplopia and pitting edema of the hands and feet (the latter a complication of curarization previously unreported\*) were the only two findings noted in the curare group but absent in the control group. In the remainder of patients displaying "toxic symptoms" it was impossible to differentiate the drug group from the control group. The dizziness of the patients on curare differed in no way from the dizziness suffered by those receiving saline solution. Similarly, drowsiness and weakness proved extremely difficult to evaluate. The severity of symptoms was grossly misleading. In 3 patients (M E S, J S and L D) toxic symptoms were sufficiently distressing to cause us considerable anxiety. Two of these patients were receiving curare, and 1 saline solution. Despite such manifestations, it was not necessary to administer prostigmine or to discontinue injections in any patient.

The opinions of physiotherapists and physical-therapy instructors, the change (if any) in spasms, the intelligence of the patient, his adjustment to his injury and his emotional stability were factors that influenced the decision whether or not he was receiving curare. Naturally, the degree of conviction concerning the type of medication being administered varied for each patient, and in some cases a definite opinion was difficult to formulate.

Seven patients with partial cord lesions received curare, and 2 received saline solution. The preponderance of the curare group was unintentional but fortunate, since it offered an opportunity to compare results of curare in patients with paraparesis and those with paraplegia. Three of these patients were incorrectly judged to be receiving saline solution. One patient was markedly relaxed, and 1 moderately so. In the group receiving d-tubocurarine none of the patients with complete transection of the spinal cord demonstrated decrease of spasm. The reduction of spasm mentioned above might be significant except for the fact that

even more pronounced relaxation occurred in some patients receiving saline solution.

A request for continuation of injections was considered a strong indication that real relief was being provided. Of those receiving d-tubocurarine, 1 patient asked that the injections be continued, whereas in the group given saline solution 2 made such a request. The 2 patients considered by the observers to be most relaxed by their injections (J M and H F) were in the group receiving saline solution. The false conviction that H F had been receiving d-tubocurarine was so strong that a heated argument ensued, and was resolved only by exhibition of the dosage schedule.

Of the 17 patients given d-tubocurarine, 9 were wrongly estimated to be receiving saline solution. Reference to Table 1 reveals that 5 of these men demonstrated no changes whatsoever attributable to medication. No symptoms were reported and spasms were unabated. One patient complained of intermittent weakness and diplopia. This particular patient, with an incomplete spinal-cord lesion and fair voluntary motion in both lower extremities, demonstrated the most violent and uncontrollable spasms observed on the Paraplegia Service at this hospital. He exhibited no change in spasms, and the mild symptoms of which he complained seemed paradoxical to the observer. Two other patients reported questionable toxic symptoms, with no evidence of improvement.

Seven of the patients given saline solution were incorrectly estimated to be receiving curare. In 3 this inaccuracy was based on the conviction that spasms had been definitely helped, 3 others exhibited no change in spasms but rather marked "toxic symptoms," and in the remaining patient spasms were increased but were accompanied by fairly severe "toxic symptoms."

It is apparent that no significant differences between the control group and the curare group were observed, and it is concluded that no beneficial effects relating to the relief of spasms in paraplegic and paraparetic patients were obtained by the intramuscular injection of d-tubocurarine in oil.

#### SUMMARY

Thirty-four patients with traumatic lesions of the spinal cord were studied in an attempt to evaluate the use of curare in spasticity due to such injuries.

Two independent series were conducted. Seventeen patients received intramuscular injections of 175 mg of d-tubocurarine chloride in oil and white wax every forty-eight hours for ten doses, and 17 were given an equal volume of physiologic saline solution intramuscularly throughout the same treatment period.

No beneficial effects relating to the relief of spasms in paraplegic or paraparetic patients were obtained by the intramuscular injection of d-tubocurarine in oil and white wax.

\*Since this manuscript was submitted for publication Grob et al. also reported a somewhat similar phenomenon accompanying intramuscular injection of d-tubocurarine chloride and these investigators attribute the dermatitis to release of a histamine-like substance.

In neither of the injection series were the observers able to estimate correctly which patients were receiving d-tubocurarine and which were receiving saline solution

The role played by suggestibility in therapy of this type of patient was clearly demonstrated

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## RECKLINGHAUSEN'S NEUROFIBROMATOSIS ASSOCIATED WITH INTRATHORACIC MENINGOCELE\*

### Report of a Case

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WE have recently encountered at operation an intrathoracic meningocele in a patient with Recklinghausen's neurofibromatosis upon whom we had operated fully expecting to find a paravertebral neurofibroma. A search of the literature on the subject of anterior intrathoracic meningocele revealed an interesting association between this lesion and Recklinghausen's disease, which we believe deserves comment since this association is not generally known.

Because of its rarity anterior intrathoracic meningocele is almost never considered in the differential diagnosis of intrathoracic tumor. Groedel<sup>1</sup> mentions the lesion in this connection in his textbook on roentgenographic diagnosis, but otherwise we have found no similar reference. Ingraham<sup>2</sup> observed no anterior intrathoracic meningoceles in the extensive

series reported in his monograph. Almost everyone is confident that a posterior mediastinal or paravertebral mass in a patient with neurofibromatosis is a tumor of neurogenic origin—in all probability, a neurofibroma. The diagnosis of intrathoracic meningocele has not been made before operation as far as we can ascertain, although the diagnosis can probably be made, as pointed out below.

Meningoceles presenting in the sacral region are the most frequent of all those projecting anteriorly. This subject has recently been reviewed by Collier and Jackson.<sup>3</sup> Anterior meningoceles may be found in the cervical and lumbar regions but less commonly than in the sacral area.

A search of the literature on the subject of intrathoracic meningocele reveals accounts of 3 cases,<sup>4-6</sup> to which may be added the case reported below. Two of the previously reported cases of intrathoracic meningocele were found in patients with neurofibromatosis. The addition of the following case accentuates the significance of this association.

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## CASE REPORT

A 41 year-old woman with known Recklinghausen's neurofibromatosis was first seen in consultation at the Boston Dispensary on May 14 1947. An intrathoracic tumor had been found in thoracic roentgenograms taken at the time of a respiratory infection 10 months previously. A postero-anterior roentgenogram of the thorax demonstrated a rounded tumor in the thorax adjacent to the mediastinum in the left paravertebral region (Fig. 1) with marked widening of the sixth intercostal space and erosion of the adjacent ribs and vertebral bodies. In addition a fairly well marked kyphoscoliosis was seen. The convexity of the scoliosis was toward the left with its apex in the region of the sixth intercostal space. Distinct erosion of the vertebral bodies and transverse processes adjacent to the tumor (Fig. 2) was also observed.

Physical examination revealed the cutaneous lesions of neurofibromatosis and the spinal deformity previously noted. Examination of the chest was negative, as was neurologic examination. Routine laboratory tests were within normal limits. A diagnosis of paravertebral intrathoracic tumor probably neurofibroma was made. It was thought that a



FIGURE 1. Roentgenogram Showing a Round Tumor Mass on the Left Side Projecting into the Left Lung Field at the Level of the Sixth and Seventh Ribs, with Perfectly Smooth Contours. There is widening of the sixth intercostal space and there are erosive bone changes of the contours of the ribs adjacent to the mass. The findings appeared to be characteristic of intrathoracic neurofibroma.

dumb-bell type of tumor with an intraspinal portion might be present, although there were no neurologic signs. Widening of the sixth intercostal space suggested encroachment of the tumor in this area characteristic of the dumb-bell type.

A left posterolateral thoracotomy was performed on May 24 and the left sixth rib partially resected.

Exposure of the tumor revealed it to be a cystic mass projecting into the thoracic cavity between the sixth and seventh ribs. Its completely smooth and globular nature was evident at once. The posterior parietal pleura was incised and the tumor was observed to be thin walled and to contain fluid. It was dissected down to its base and found to have a neck 3 by 4 cm in diameter which came out of the sixth intervertebral foramen. The diagnosis of meningocele was suspected, and 250 cc of clear spinal fluid normal to character was aspirated from the sac. Complete dissection

of the meningocele was possible down to the leptomeninges of the spinal cord because of the great separation of the neural arches and consequent enlargement of the intervertebral foramen. The meningocele was incised, and its interior was found to be continuous with the subarachnoid space. Adequate visualization of the spinal cord was obtained. No major nerves were contained in the sac, which was excised at its neck. The dura was closed with a layer of interrupted silk sutures. To prevent the leakage of spinal fluid into the



FIGURE 2. Film of the Thoracic Portion of the Spine Showing a Kyphoscoliosis with Convexity toward the Left, the Point of Greatest Convexity Being at the Level of the Sixth Intercostal Space.

There is marked erosion of the lateral and anterior surfaces of the fifth, sixth and seventh thoracic vertebrae and some erosion of the transverse processes of the sixth and seventh vertebrae on the left side together with the previously mentioned erosive changes of the ribs.

thoracic cavity a pedicle graft of the intrinsic dorsal musculature was fashioned and sutured to the edges of the intervertebral foramen. This seemed to fit snugly and to fulfill a real need to ensure a satisfactory support for the dorsal closures. The thoracic closure included the use of a steel suture for the approximation of the fifth and seventh ribs which were widely separated because of the spinal deformity. Catheter drainage of the thoracic cavity was employed for 48 hours. Convalescence was uneventful, and the patient was discharged on the 21st postoperative day. Figures 3A and 3B show lateral roentgenograms taken before and after operation to the latter film the previously noted area of density from the tumor is absent.

Tissue examination of the meningocele sac revealed a cyst wall composed of nerve tissue, pia arachnoid and dura showing fibrosis. The tissue findings were consistent with congenital malformation involving the three structures: nerve tissue, pia arachnoid and dura with cyst formation.

The final anatomic diagnosis in this case was simple meningocele; the wall contained portions of all layers of the leptomeninges.

## PREVIOUSLY REPORTED CASES

In 1933 Pohl<sup>4</sup> reported the case of a forty-seven-year-old woman with Recklinghausen's disease who came to operation with a diagnosis of solid tumor of the mediastinum, probably neurofibroma. At operation a meningocele was found on the right side, which arose at the apex of a kyphoscoliosis in a manner similar to that in the case presented above. Pohl noted a high degree of widening of the intervertebral foramen and called attention to the incidence of spinal-column deformity in Reckling-

meningocele, which was also associated with marked kyphoscoliosis. There was considerable enlargement of the intervertebral foramen and marked erosion of the vertebral bodies.

The third case of intrathoracic meningocele that we have found in the literature was reported by Ameuille, Wilmoth and Kudelski<sup>6</sup> in 1940. A large intrathoracic tumor on the right side, which seemed to emerge between the eighth and ninth thoracic vertebrae and to be situated paravertebrally, was discovered in a forty-eight-year-old woman. Thoracotomy was performed, and a probable diagnosis of

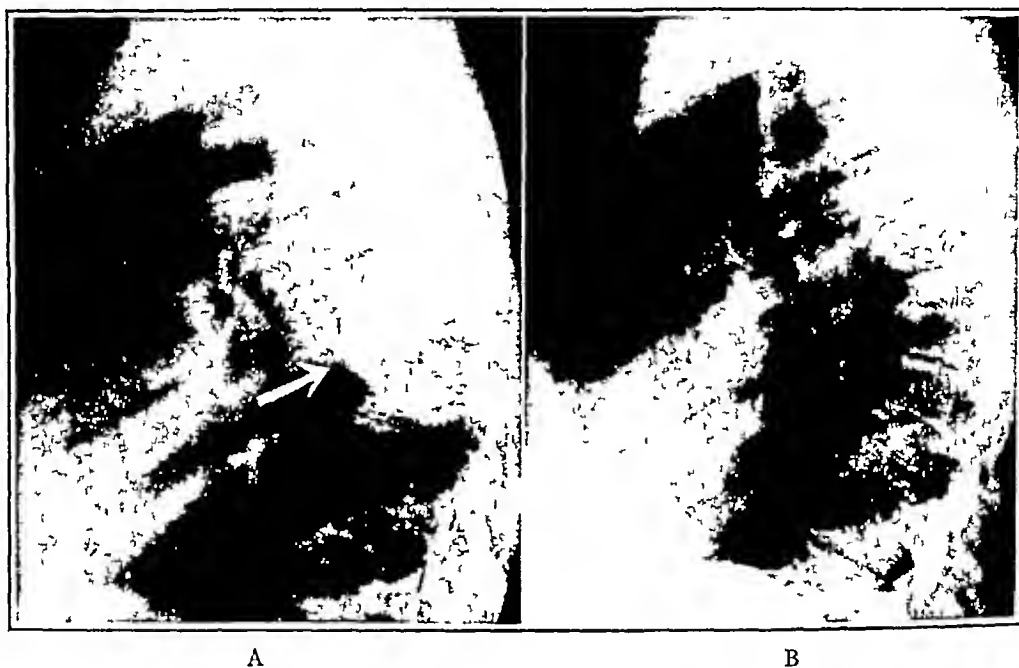


FIGURE 3 Roentgenograms of the Thoracic Area

*The lateral view (A) shows the mass demonstrated in Figure 1 to be situated far posteriorly, the anterior margin projecting scarcely beyond the anterior surface of the spinal column. B shows a postoperative film of the thorax after excision of the meningocele.*

hausen's disease. The operative and roentgenologic findings were confirmed at autopsy, since this patient died of empyema during the postoperative period.

In 1938 Schüller and Uiberall<sup>5</sup> reported the findings in the case of a fifty-six-year-old man with Recklinghausen's disease and a right-sided intrathoracic tumor who came to post-mortem examination. They had previously performed myelographic studies after a suboccipital injection of lipiodol and had perhaps used the only method of diagnosis for intrathoracic meningoceles. Retention of lipiodol was noticed in a dimple at the level of the sixth dorsal vertebra, and, in addition, a spot of lipiodol was seen outside the spinal column and presumably inside the mediastinal tumor. The authors seem to have made the correct diagnosis before death. The patient died after resection of the posterior roots of the sixth, seventh and eighth dorsal nerves, performed for relief of pain. Autopsy disclosed a

hydatid cyst was made at the time of operation. The cyst was punctured, and the orifice packed with gauze. Death occurred from empyema and loss of spinal fluid in the pleural cavity. At post-mortem examination the cyst was identified as a meningocele and the cause of death was attributed to loss of spinal fluid and infection of the pleural cavity. Presumably, this patient did not have Recklinghausen's disease since no mention was made of it in the report.

## DISCUSSION

In the cases of intrathoracic meningocele reported in the literature it is of interest that 2 patients had Recklinghausen's neurofibromatosis and the meningocele was associated with kyphoscoliosis and seemed to arise at the apex of the deformity. The lesion may be congenital, since it is associated with congenital anomalies. Sharpe and Young<sup>7</sup> found cerebral meningocele, spina bifida.



cranial defects and defects in the digits in many cases. Thannhauser,<sup>8</sup> in his review of Recklinghausen's disease, refers to the frequency of developmental anomalies, as do Carriere et al.<sup>9</sup> in their monograph on the subject. Intrathoracic meningoceles, however, have not been specifically mentioned in these reviews. The incidence of paravertebral neurofibromas with or without intraspinal segments (dumb-bell tumors) in patients with Recklinghausen's disease is not exactly known, but it is our opinion that intrathoracic tumors of neurogenic origin are not common.

Blades,<sup>10</sup> in a review of 109 patients with mediastinal tumors operated upon, found thirty tumors of neurogenic origin none of which, presumably, were associated with Recklinghausen's disease. In a review of a collected series of 105 cases of neurogenic tumors by Kent and his co-workers,<sup>11</sup> only 4 patients had Recklinghausen's disease. The relatively low incidence of intrathoracic neurofibromas in patients with Recklinghausen's disease should, therefore, bring the possibility of intrathoracic meningocoele into greater prominence in the differential diagnosis. The incidence of malignant changes was 41 per cent in the cases of intrathoracic neurogenic tumors reported by Kent et al.<sup>11</sup> The uncertainty of the diagnosis represents an indication for operation in these patients. On the other hand, if the diagnosis of intrathoracic meningocoele can be made, operation might be avoided, particularly in poor-risk patients with Recklinghausen's disease.

Intrathoracic meningoceles actually arise as lateral structures, usually projecting through the intervertebral foramina, and then pass anteriorly between the ribs to project paravertebrally into the thoracic cavity, pushing the posterior parietal pleura forward. Their course is quite similar to that of the dumb-bell shaped tumors, which project inside the spinal column, producing a compression of the cord, and into the thoracic cavity.

Naffziger and Brown<sup>12</sup> have called attention to the incidence of the leaking of spinal fluid into the pleural cavity after removal of dumb-bell tumors. The same complication, which may follow operation for meningoceles, was responsible for death in at least 1 of the reported cases.

It seems possible that the diagnosis of intrathoracic meningocoele can be made by myelography, since Schüller and Uiberall<sup>13</sup> have presented evidence that meningoceles in this region can be partially filled and visualized. Eichler<sup>14</sup> was apparently the first to visualize an anterior sacral meningocoele with this method. In patients with Recklinghausen's disease, marked kyphoscoliosis and an intrathoracic tumor, the diagnosis of meningocoele should be entertained and a myelogram performed.

#### SUMMARY

A case of Recklinghausen's neurofibromatosis and an intrathoracic meningocoele is reported.

Of the 3 previously reported cases of intrathoracic meningocoele, 2 occurred in patients with Recklinghausen's disease. The presence of intrathoracic meningocoele should be borne in mind whenever one encounters a patient with Recklinghausen's disease and roentgenologic evidence of an intrathoracic tumor in the paravertebral region, particularly if there is erosion of the vertebrae and ribs and kyphoscoliosis. The position and progression of meningoceles from the spinal column proceed in a lateral and anterior direction, usually through the intervertebral foramen in a manner similar to that of dumb-bell tumors. Meningoceles, however, do not produce spinal-cord compression and neurologic signs. The operative approach for intrathoracic meningoceles is transthoracic. The management of dural closure presents the same problem that exists in the removal of dumb-bell tumors. Closure of the dura must be tight, and in the case reported above, a pedicle graft of the intrinsic muscles of the back was used to reinforce the dural closure.

In the previous reports on intrathoracic meningoceles, all the patients died at operation — 1 after resection of the posterior roots of the dorsal nerves for pain, and the others after direct operative attack on the meningocoele, loss of spinal fluid into the pleural cavity and empyema being the cause of death in these 2 cases.

Myelographic studies may be helpful in certain patients with Recklinghausen's neurofibromatosis and intrathoracic tumors. On the chance that a meningocoele is present, the examiner should try to fill such tumors with opaque mediums by gravity and position changes during myelography in an attempt to demonstrate continuity of the tumor with the subarachnoid space. Failure to fill the tumor by either air or opaque mediums, however, does not disprove a diagnosis of anterior meningocoele.

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## EOSINOPHILIC GRANULOMA\*

## Report of a Case with X-ray Evidence of Rapid Progression

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**E**OSINOPHILIC granuloma is a rare disease of bone that has only recently been described as an entity. Approximately 45 cases have been reported in the literature. The condition was simultaneously described in 1940 by Lichtenstein and Jaffe<sup>1</sup> and by Otani and Ehrlich.<sup>2</sup> The former employed the term "eosinophilic granuloma," and the latter "solitary granuloma of bone," to describe the same pathologic process. Otani and Ehrlich's term has largely been dropped, because the lesions are not always solitary and "eosinophilic granuloma" gives a connotation that adds specificity to the mental picture of the lesion. Two previous reports<sup>3,4</sup> in the literature described lesions that, in the light of present knowledge, were probably the same disease as eosinophilic granuloma. It remained for these four authors, however, to collect several cases and present the clinical, x-ray and pathological picture as a distinct disease.

In 1942 Farber<sup>5</sup> and later Green and Farber<sup>6</sup> suggested that eosinophilic granuloma was not in itself a specific disease but was one phase of the progression of xanthomas that ultimately developed into Hand-Schüller-Christian's disease. They presented cases that ran the gamut from what has been described as typical lesions of eosinophilic granuloma to the clinical picture of exophthalmos, diabetes insipidus and lesions of the cranial fossa. In 1944 Jaffe and Lichtenstein<sup>7</sup> reviewed the subject and agreed that eosinophilic granuloma, Letterer-Siwe's disease and Hand-Schüller-Christian's disease were allied, but emphasized the inflammatory aspect. A clinical and morphologic transition from eosinophilic granuloma to Hand-Schüller-Christian's disease has been observed by Engelbreth-Holm et al.<sup>8</sup> in 5 cases. It is not the purpose of this paper to take sides in this controversy. There are many who agree with Green and Farber<sup>6</sup> that this is a metabolic dyscrasia. Others consider it to be an inflammatory disease, possibly infectious, although no etiologic agent has yet been isolated.

## CLINICAL PICTURE

Eosinophilic granuloma occurs more frequently in male than female patients. It is seen most commonly in children and young adults. About 80 per cent of the cases reported in the literature were in children. It is extremely rare over the age of twenty-five. Otani and Ehrlich,<sup>2</sup> in their original paper, reported a case in a thirty-five-year-old man. Versiani, Figueiro and Junqueira<sup>9</sup> reported a case in a fifty-year-old woman who developed a pathologic fracture in the left tibia, biopsy of which showed typical eosinophilic granuloma interspersed with areas of xanthomatous tissue. This woman in addition had diabetes insipidus, although she had no exophthalmos and no cranial defects by x-ray study. She may thus represent an in-between phase as described by Green and Farber.<sup>6</sup>

The disease has certain other characteristics in addition to the age and sex incidence. The lesion may be single or multiple and may involve any of the bones except those of the hands and feet. The ribs and skull, however, are the favorite sites. The long bones are next. One lesion has been reported in the clavicle.<sup>10</sup> X-ray films show rarefied, punched-out areas, which may erode the cortex and in which pathologic fractures may occur. New bone formation may appear secondary to these fractures. There are no associated generalized symptoms, such as fever, malaise and those referable to the gastrointestinal or cardiorespiratory system. Symptoms that are present are due entirely to the local lesion. In the case reported below there was local pain and tenderness. Certain lesions in the skull have led to some of the more bizarre neurologic manifestations.<sup>11</sup> Laboratory examinations are of no help in making a diagnosis. The white-cell count and the morphology of the blood cells are usually normal. Occasionally there is a slight eosinophilia. The blood calcium, phosphorus, acid and alkaline phosphatase and cholesterol levels are normal.

Gross examination of the lesions shows soft granulation tissue, which in places is hemorrhagic, in others yellowish and in still others necrotic, frequently with some destruction and replacement by granulomatous tissue. Microscopically, there are sheets of eosinophils along with phagocytic mono-

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nuclear and multinuclear histiocytes. Round-cell perivascular infiltration may be prominent.

The case reported below is interesting from two points of view. The patient, except for the woman of fifty described by Versiani et al.,<sup>9</sup> is to our



FIGURE 1 X-ray Film Taken on April 1 1946 Showing a Cystic Lesion of the Right Seventh Rib

knowledge the oldest thus far reported. What is probably of more interest are the x-ray films. In eosinophilic granuloma the duration of symptomatology is often only a few months. The disease has therefore been considered to be rapidly pro-

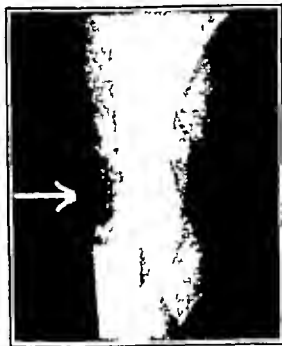


FIGURE 2 X-ray Film Taken on April 29, 1946 Showing Erosion of the Cortex of the Rib

gressive. In no previously reported case, however, has this feature been so graphically demonstrated. In two months what originally appeared to be a small benign cyst, measuring 0.5 cm in diameter, became a process that destroyed about 3 cm of rib

Most authors agree that although the usual treatment is local excision and curettage, the lesion can be successfully handled by small doses of x-ray therapy or even by no treatment at all.<sup>6-11</sup> One would have to possess considerable fortitude to have maintained a laissez-faire policy when presented with these x-ray films, not knowing what the lesion showed microscopically. It is our opinion that it is wise to perform a biopsy of any lesion before x-ray treatment or radical or conservative surgery is considered.

#### CASE REPORT

J. L., a 39 year-old shipper entered the hospital on May 18, 1946, complaining of constant pain and soreness in the right anterolateral portion of the chest. About 1½ years before entry he had fallen against a truck and hurt the right side



FIGURE 3 X-ray Film Taken on May 31 1946 Showing Marked Destruction of the Ribs in Two Months

of the chest which had been strapped with adhesive tape, and the symptoms had subsided in 1 week. He was then well until 1½ months before entry when he was seized by a pain in the right side of the chest while lifting a heavy packing case. X-ray films taken in another clinic disclosed a small cystic lesion of the seventh rib (Fig. 1). About 4 weeks later a second x-ray film showed an increase in the size of the lesion (Fig. 2). There was no history of respiratory complaints or of any generalized symptoms. A review of the system was negative.

The past history revealed an attack of rheumatic fever in 1925, with no early or late sequelae.

Physical examination showed a well developed and well nourished man in no acute distress but complaining of soreness in the right anterior axillary line well localized to the seventh rib. There was moderate tenderness in this area, and a depression could be felt in the rib but no soft tissue mass. Examination otherwise was negative.

Examination of the blood revealed a hemoglobin of 18 gm. and white-cell counts of 8600 and 9200 with 55 per cent neutrophils, 34 per cent lymphocytes, 8 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. Examination of the urine, including tests for Bence-Jones protein, were negative. A Mazzini test was negative.

X-ray films showed a great deal more destruction of the seventh rib than had been present at the examination 1 month previously. In addition there was a fracture through the



FIGURE 4 Enlargement of Figure 3, Showing Detail of the Destructive Process

lesion (Fig 3 and 4). Films of the long bones, skull and pelvis were completely normal.

While in the hospital the patient had an afebrile course. In the early part of his stay the x-ray films taken prior to



FIGURE 5 Postoperative X-ray Film, Showing Partial Rib Resection

admission were not available. For this reason there was considerable discussion about the nature of the lesion presented by the physical findings and x-ray examination in this hospital.

The possibilities mentioned ranged from Ewing tumor and osteogenic sarcoma to multiple myeloma, osteomyelitis and eosinophilic granuloma. When the other films became available, it was generally believed that the lesion was benign but that exploration was warranted in view of the rapid progression of the process.

On June 12, under endotracheal nitrous oxide, oxygen and ether anesthesia, a partial rib resection was carried out. On exposure of the lesion no invasion of the surrounding tissue was found. There was a pathologic fracture through the rather thin bone. Frozen section was made of the tissue obtained at operation and reported as eosinophilic granuloma. The patient made a smooth postoperative convalescence and was discharged from the hospital on June 19.

At follow-up examination 6 months later, the patient was asymptomatic. Physical examination was negative, and recheck x-ray films were normal (Fig 5).

Pathological examination of the specimen revealed a segment of rib 7.5 cm long, 1.8 cm wide and 0.6 cm thick at

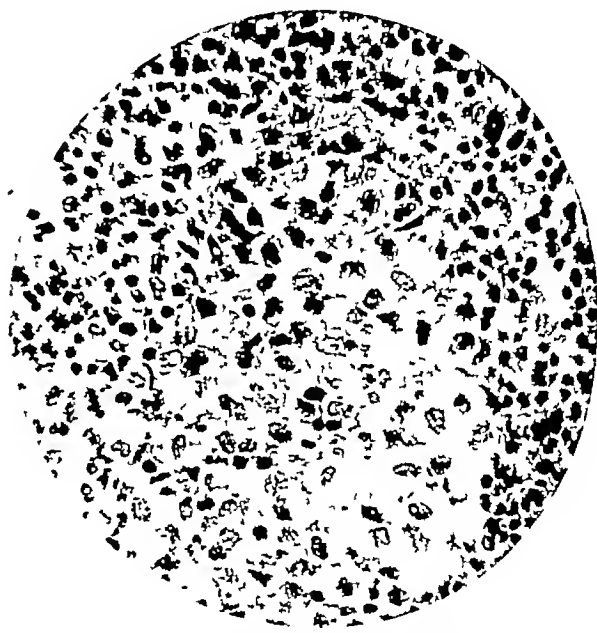


FIGURE 6 Photomicrograph of a Typical Section, Demonstrating Eosinophilic Cells at the Periphery and Histiocytes in the Center, a Few of Which Show the Typical Indented Nucleus

the anterior end, and 1.5 cm wide and 0.5 cm thick at the posterior end. The following is a transcription of the pathological report.

There is a slight fusiform dilatation of the central portion through which there is a transverse pathologic fracture, with loss of continuity of the bone. At the widest point the rib is 2.0 cm wide and 1.0 cm thick. The widened part is occupied by an almond-shaped mass of soft, gray-brown tissue, 3.1 by 1.7 by 0.9 cm in diameter, that is fairly well demarcated from the bone at the ends. Anteriorly, the cortex is completely destroyed over the mass, which is covered only by bulging red periosteum. Posteriorly, new white callus, 2 mm or more thick, has formed over the old cortex, and appears to be infiltrated with gray-brown tissue in its inner portion. This tissue extends grossly only as far as 1.7 cm from the anterior end and 2 cm from the posterior end of the specimen. It perforates the cortex at the posterosuperior edge of the rib, but does not appear to pass beyond or through the periosteum at any point.

Microscopical examination of the soft yellow-brown central tissue shows vascular granulation tissue containing follicle-sized foci of loosely arranged histiocytes with large pale nuclei, occasional multinucleate (giant) cells, massive infiltration with eosinophils and lymphocytes in

equal or lesser numbers (Fig 6). There is an area of necrosis centrally. Peripherally there is a transition into dense scar tissue with fibrous endarteritis. Perivascular lymphocytic infiltration and macrophages containing old blood pigment extend into the adjoining skeletal muscle. The diagnosis was eosinophilic granuloma of bone (benign).

### SUMMARY

The literature on eosinophilic granuloma is briefly reviewed.

A case in a thirty-nine-year-old man is presented. X-ray films showed a very rapid progression of the disease in the course of two months.

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## A SEVERE REACTION TO TETRAETHYLAMMONIUM CHLORIDE

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**T**ETRAETHYLAMMONIUM salts have been found to block efferent autonomic impulses at both the sympathetic and parasympathetic ganglions.<sup>1,2</sup> Because of this action, the drug is being employed in a variety of clinical studies. The effect of tetraethylammonium ion in man has been described by Lyons and his associates,<sup>3-5</sup> who have administered the drug over a thousand times with "very few serious effects." They make particular reference to the occasional profound fall in blood pressure and transient vascular collapse in patients with malignant hypertension who have received tetraethylammonium parenterally. Otherwise, there has been no report of a severe untoward reaction to this drug. In the course of studies on hypertensive patients and on intestinal motility at the Massachusetts General Hospital,<sup>6</sup> tetraethylammonium ion had been given nearly a hundred times before a severe reaction occurred. The purpose of this communication is to report the reaction in detail.

### CASE REPORT

A 37-year-old nulliparous housewife entered the hospital for the investigation of abdominal pain. She had undergone five abdominal operations for pelvic inflammatory disease, which had resulted in the cessation of menses and the occurrence of hot flashes in 1934. Several years later she began to have attacks of severe epigastric and right upper-quadrant pain which radiated through to the tip of the right scapula and to the right shoulder. These attacks were accompanied by nausea and vomiting. Cholecystectomy revealed an inflamed gall bladder but no gallstones. She felt well for

18 months but thereafter continued to have episodes of pain similar to those preceding the cholecystectomy. In 1942 she was seen for the first time at this hospital, where a common duct exploration was advised, but was declined by the patient. At that time the blood pressure was 120/70. After this admission she had infrequent pain. In 1946 frequent attacks of epigastric and right upper-quadrant pain radiating to the right scapula and shoulder again developed. During such an attack accompanied by severe vomiting she re-entered the hospital.

Physical examination was remarkable only for an olive blot of the skin and multiple abdominal scars. The blood pressure was 110/70. Laboratory findings including a gastrointestinal series, barium enema, intravenous pyelogram, duodenal drainage, serum amylase and all liver-function tests were within normal limits. Because of the obscure nature of the pain, intestinal motility studies were done by one of us (W. P. C.) using distensible balloons placed to the upper portion of the small bowel. The blood pressure previous to the test averaged 105/70. The intravenous administration of 0.6 mg of atropine abolished the intestinal contractions and relieved the abdominal pain. The distention of a balloon immediately below the ligament of Treitz reproduced the right upper-quadrant pain but without its usual radiation.

On the following morning the patient was given tetraethylammonium chloride with the intestinal balloons in place, to observe the effect on the pain of abolishing intestinal contractions with this agent. Before the injection the blood pressure and pulse rate were recorded at 2 minute intervals for 10 minutes. The blood pressure averaged 120/80 and remained nearly constant. The average pulse rate was 75. The abdominal pain was then of moderate to severe intensity. Tetraethylammonium chloride, to a dosage of 230 mg was given intravenously at a rate of 100 mg per minute. The patient was hyperventilating slightly immediately before the injection. This increased markedly during the administration and immediately thereafter. Within 1 minute after the injection had been begun, the intestinal contractions ceased with complete relief of pain. At that time the blood pressure was 115/85. After 230 mg of the drug had been given, the blood pressure fell to 75/55, with a pulse rate of 80. Because of this decrease the remainder of the contemplated dosage of 300 mg was not given. Within the next 30 seconds the patient complained of numbness and weakness, became dyspneic and pale, and then sat up exhibiting ineffectual,

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gasping respirations of an alarming nature. She later stated that at that time a large flash of light had appeared before her, after which "everything went black." The blood pressure was 68/48, and the pulse rate 96. Epinephrine (0.2 cc of a 1:1000 solution) was given intravenously, after which the blood pressure rose to 102/76 and the pulse rate to 108 per minute. The respiratory distress was relieved, and she felt better. Within 4 or 5 minutes the blood pressure again fell to 68/54, the respiratory distress returned, and 0.1 to 0.2 cc of epinephrine was again given, in addition to oxygen by mask. During the next 15 minutes this sequence of events was repeated three times. Because the pulse rate rose to 140, neosynephrine was substituted for epinephrine on a subsequent occasion, and an intravenous infusion of 1000 cc. of 5 per cent dextrose in water was started. Fifteen minutes after the administration of tetraethylammonium chloride the patient complained of inability to move the legs, which persisted for 20 minutes. At about the same time she had well marked carpopedal spasm and a positive Chvostek sign, which were dispelled by rebreathing. Thirty-five minutes after the injection of tetraethylammonium chloride, intestinal contractions returned to their previous normal level. Nevertheless, the blood pressure remained at 70/40, with a pulse rate of 140. Over the next 2-hour period the blood pressure was hardly obtainable, and the patient continued to complain of marked weakness. An electrocardiogram revealed a perfectly regular rhythm at a rate of 190, which did not vary with carotid-sinus pressure. Small upright P waves immediately preceding the QRS complexes could be seen only in the special auricular Lead 3. The duration of the QRS complexes was 0.08 second, and they were of small amplitude. The ST segments were sagging in Leads 2 and 3, and the T waves were essentially flat in all conventional limb leads. These findings were interpreted as representing rapid paroxysmal auricular tachycardia. The arrhythmia persisted for 18 hours, reverting to normal rhythm at a rate of 110 per minute after a test dose of 75 mg of quinidine lactate given intramuscularly. Throughout the acute episode the patient remained fully conscious, and the skin remained dry.

During the afternoon of this severe reaction, the patient received 600 cc. of plasma and 500 cc. of whole blood, after which the blood pressure stabilized at 90/60. Despite the reversion to a normal heart rate and rhythm, the blood pressure remained at levels averaging 80/65 on the 1st day, 80/60 on the 2nd day, and 80/55 on the 3rd day after the administration of tetraethylammonium chloride. Subjectively, the patient gradually improved, and the blood pressure rose to 90/60 on the 9th day at the time of discharge from the hospital.

One month later the patient was readmitted for further studies, which failed to elucidate the cause of the severe reaction to tetraethylammonium chloride. During this admission the blood pressures averaged 100/65. Liver-function studies were again negative. An extensive laboratory evaluation of the endocrine status, including, among other procedures, a Wilder test, determinations of 17 ketosteroids, 11 oxysteroids, serum sodium and potassium, and inspection of the rate of axillary-hair growth, revealed values within normal limits except for a basal metabolic rate averaging -22 per cent and an elevated urinary output of follicle-stimulating hormone (the last finding was consistent with the menopausal state). The diagnoses on discharge were possible biliary dyskinesia, menopausal syndrome and psychoneurosis. At a subsequent laparotomy the common duct was normal except for a somewhat constricted sphincter of Oddi, multiple adhesions involving the upper portion of the small intestine and a dilated duodenum.

### DISCUSSION

It appears that the administration of 230 mg of tetraethylammonium chloride given to this patient

produced a severe immediate reaction, which was characterized by profound hypotension and an alarming degree of respiratory distress. The hyperventilation may have been on the basis of anxiety, but Lyons et al.<sup>4</sup> described 4 female patients who developed sudden hyperventilation after the administration of this drug. They also reported transient inability to move the legs, a feature that this patient presented. The persistence of hypotension for several days cannot be definitely ascribed to the drug, since the return of intestinal contractions occurred in the usual time,<sup>8</sup> suggesting that the tetraethylammonium ion had been largely eliminated. The paroxysmal tachycardia could be attributed to the drug, to the use of the vasopressor drugs or to the patient's unstable emotional state.

The manner in which such an unfortunate reaction to the drug may be avoided by proper selection of cases is beclouded by the many features that characterized this patient. She was a small, asthenic, emotionally unstable woman with a low-normal blood pressure, who had symptoms and laboratory evidence suggestive of the menopause and of hypothyroidism. Whatever the mechanisms involved, the fact remains that the patient experienced an untoward reaction to the administration of tetraethylammonium chloride of such severity as to cause grave concern. The possible occurrence of such a reaction is called to the attention of those using the drug or contemplating its use.

### SUMMARY

The action of tetraethylammonium chloride in man is briefly discussed, and the literature briefly reviewed.

A case of a severe untoward reaction to the drug is reported.

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## MEDICAL PROGRESS

### TECHNICAL ADVANCES IN PHYSICAL MEDICINE

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IN RECENT years those concerned with developments in the field of physical medicine have rightly emphasized the need for fundamental research, and a number of investigative and training centers have been established with this in mind.<sup>1</sup> Reviews of current research in physical medicine have been the subject of previous reports in this series<sup>2</sup> and elsewhere.<sup>3</sup> Physical medicine is best known, however, for its therapeutic activities, and certain developments in technic constitute the basis of the following report.

#### PROGRESSIVE-RESISTANCE EXERCISES

Therapeutic exercise can be considered the most frequently utilized and probably the most valuable single procedure in this specialty. It is accordingly of some significance to report an advance in technic of application. DeLorme,<sup>4</sup> while serving in the Army Medical Corps, reported the successful adaptation of the system of muscle training of professional weight lifters to restore maximum function to weak, atrophied muscles after certain types of disease and injury.

The basic principles of this system may be simply stated. To produce power in a muscle—that is, ability to lift heavier loads—the training exercises should be with heavy resistances and few repetitions. In contrast, endurance is developed by low-resistance exercises with frequent repetitions as with stationary bicycle riding. This method of heavy-resistance, low-repetition exercising was found by DeLorme to develop muscular power to a remarkable degree, as evidenced by ability to lift greater weights and by actual muscular hypertrophy according to circumferential measurement. The speed of such muscular development was much more rapid than that observed with the conventional type of exercises.<sup>4</sup>

#### Exercise Program

The exact exercise load for any patient is based on his maximum effort as recorded once a week on the test day. At the beginning of the program weights are gradually added to the load upon the exercised muscle until the maximum that can be moved ten times through the full range of motion is determined. This is designated as the 10-repetition maximum (10 R M). The exercise work schedule for the following week is based on this determination.

In the original papers by DeLorme<sup>4</sup> the work program consisted of a series of exercises, usually with seven to ten sets of different weight lifts repeated ten times each as the daily exercise stint. Exercise was started with lighter loads and ended with ten lifts at the 10-repetition maximum. Once a week on the test day the 10-repetition maximum was determined, which usually increased, and also the 1-repetition maximum (1 R M), or the greatest weight that could be lifted once through the full range of motion. In some cases, as in joint instability, incomplete healing of wounds or arthritis, the determination of the 1-repetition maximum was omitted. The usual weekly schedule consisted of the daily exercises with the same prescribed weights and frequencies until the test day, after which there were two days without any exercise. Only one exercise period a day was permitted.

#### Results

In the first series of patients reported by DeLorme emphasis was placed on development of power of the quadriceps muscle. The types of cases treated included unstable knees from tears of cruciate and collateral ligaments and after removal of the menisci, as well as fractured femurs and patellas, recurrent dislocations of the patella and atrophy of the quadriceps from prolonged immobilization from fractures in the vicinity of the knee joint or other injuries necessitating immobilization. He found that in a series of patients the average time required to restore normal power to the extensor mechanism of the knee was nineteen days. It was also observed that such heavy-resistance exercises were more satisfactory than weight-bearing exercises before full muscle strength had been regained. At the same time increase in the range of knee motion was coincident with the increase in muscular power, the range of motion closely approaching normal unless gross damage of articular surfaces was present.

This principle of relatively maximal resistance with minimal repetitions as advocated by DeLorme has been put to clinical test in a variety of conditions beyond those of trauma to bones and joints. Preliminary studies in patients with residual weakness from poliomyelitis have indicated that muscle groups previously with power of only 20 to 50 per cent of normal may be able to increase their functional capacity to a significant degree.<sup>5</sup> This was found true even in cases of long standing paresis.<sup>6</sup>

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when careful measurement of muscle strength was made by means of ergographic tracings, maximum-effort test, spring-gauge test and circumferential measurement of muscular volume. The rapidity of improvement in muscular strength in these long-standing cases of poliomyelitis was, as might be expected, considerably slower than that in patients suffering only from weakness of disuse atrophy. It was also observed that improvement in muscle strength was not sufficient to cause an increase in grading according to the usual manual scale, although significant changes were observed in the maximum-strength tests and ergographic tracings. It was further noted that the patients reported coincident improvement in functional ability in ordinary tasks such as ability to walk greater distances without fatigue.

### *Physiologic Studies*

As might be anticipated, this method of exercise was soon investigated by physiologists on normal persons, particularly because of the empiric origin and nature of the training regime employed. At the Baruch Center of Physical Medicine at the Medical College of Virginia a group of normal persons were subjected to a period of training with heavy-resistance exercises following the DeLorme technic involving the motions of knee extension and elbow flexion.<sup>7</sup> In this study the daily work unit consisted of 70 to 100 contractions divided into bouts of 10, with rest pauses between the series of repetitions as originally proposed by DeLorme, the last series not surpassing the 10-repetition maximum. The study period consisted of not less than four weeks of exercise, and the criteria of improvement were obtained by the maximum efforts put out on the test days — namely, the 10 R M or the 1 R M. The results obtained suggested that the most important single element leading to increase in work output was the will to perform a physiologic maximum effort. Daily exercise of this sort was found to produce a significant increase in work done on each weekly test day, and the improvement in work capacity under such a program of heavy-resistance exercise was rapid, for strength more than doubled in four weeks of systematic training. The increased work capacity was also found to continue during a post-exercise period, which exceeded in duration the initial period of training, in fact, the ability to perform work might continue to improve after the cessation of systematic training, suggesting a type of motor learning including extension of the psychologic end point of fatigue.

Further studies of a similar nature from the same laboratory are of considerable interest.<sup>8</sup> In another experiment normal adults were subjected to a series of heavy-resistance exercises to a single upper or lower extremity, and the changes in the contralateral limb were observed. Such exercises, which rapidly

increased the strength of the exercised limb, had a corresponding effect on the contralateral unexercised extremity, although the results were less marked. It was believed that the determining factor in this so-called "cross education" was the severity of the effort evoking the response rather than the duration of the exercise. It was suspected, however, that the unpracticed side received many reflex stimuli, which acted upon it to evoke widespread synergistical contraction. The results of this study suggested that such "cross education" might serve as a useful therapeutic tool in cases in which volitional control is unilaterally defective or in which contralateral muscle groups are rendered temporarily inaccessible through immobilization.

### *Technic of Exercise*

Because so little detailed information is available concerning the use of this exercise equipment, particularly as applied to the weaker grade muscles, some of the important technical aspects are discussed. In relation to counterbalancing in exercises two terms must be defined: the "exercise load" and the "muscle load." The exercise load is the load that is placed upon the weight pan of the apparatus and does not necessarily refer to the resistance placed upon the muscle, since in some cases it is used as counterbalance. The muscle load is the actual resistance the muscle must overcome during the exercise. For strong muscles the muscle load includes the weight of the extremity and the exercise load. For weak muscles the muscle load is still near the maximum for that muscle but less than the weight of the extremity, for the exercise load serves as a counterbalance. When the exercise load is used as counterbalance it never exceeds the weight of the extremity, thus producing passive motion, but is always within the range necessitating maximum voluntary effort. The term "load-assisting exercises" has been applied to procedures in which the exercise load assists the muscle, and "load-resisting exercises" to those in which the load resists the muscle.

With load-resisting exercises the work increase for the week is based, as mentioned above, on the 10-repetition maximum. With load-assisting exercises the exercise routine is based on the 10-repetition minimum, which is determined by tests for the smallest load on the weight pan that still permits the muscle to perform not more than 10 repetitions while doing a load-assisting exercise. As muscle strength increases it can be seen that the exercise load will decrease. The opposite is true in case of load-resisting exercises. It has also been found when dealing with these weaker grades of muscles that the daily exercise prescription, instead of being from 70 to 100 repetitions, may be reduced to three sets of 10 repetitions or even less. An approximate scheme for determining exercise loads is as follows:<sup>9</sup>

**Load-resisting exercises**

First set of 10 repetitions  
Second set of 10 repetitions  
Third set of 10 repetitions

A half of 10-repetition maximum  
Three fourths of 10-repetition maximum  
10-repetition maximum

**Load-assisting exercises**

First set of 10 repetitions  
Second set of 10 repetitions  
Third set of 10 repetitions

Takes the 10-repetition minimum  
One and a half times the 10-repetition minimum  
10-repetition minimum

With improvement in strength it is possible simply by readjusting the pulley arrangement to change from load-assisting to load-resisting exercises, thus continuing the principle of progressive resistance exercises with near maximum resistances of few repetitions at all times (Fig 1)

**MICROWAVES ("RADAR")**

High frequency electrical currents have been used in medicine and surgery for over fifty years. It was demonstrated, particularly by d'Arsonval, that frequencies above 10,000 cycles per second produce no evident effect beyond that of heating the tissues through which they pass. Frequencies in the neighborhood of 1,000,000 to 3,000,000 cycles per second or long-wave diathermy began to be employed about 1900 and are still in use. Over 10 years ago the frequencies were increased to clinical generators to the neighborhood of 10,000,000 cycles with a wavelength of 30 meters or less (short-wave diathermy). Then frequencies of 100,000,000 cycles were produced, or wave lengths of 3 meters. They were called ultra short-waves. Electronic developments have now made it possible to apply frequencies of 3,000,000,000 cycles of wave lengths of 10 cm., which have been called microwaves and are related to radar of wartime prominence. Although radiations of such frequencies and wave lengths were produced before the war, it was not until recently that their possible usefulness in medical practice could be determined.

**Physical Characteristics**

Certain physical properties of microwaves can be contrasted readily with radiations of lower frequency in the radio-frequency spectrum. Microwaves have optical properties, for they can be reflected, refracted and diffracted. They can also be focused by suitable lenses and reflectors much as the beam of a searchlight. Microwaves may be selectively absorbed, but the biologic significance of this is still unknown.

This high-frequency energy cannot be transmitted from and to antennae in the usual fashion of a lower frequency but is transported along hollow pipes or coaxial cables, known as wave-guides, which must be carefully designed according to the frequency used. Certain meteorologic conditions in nature may act as wave-guides, and during the war the pulse-echo system was used to determine the location of enemy targets with radar. Therapeutically, however, energy is continuously rather than intermittently transmitted.

It has been found that the absorption factor of water at 100°F for microwaves at a frequency of

2450 megacycles per second — that assigned by the Federal Communications Commission — was approximately seven times greater than that of the usual short-wave frequencies of 27 megacycles. There is thus experimental physical evidence of the possible efficiency of this type of energy for heating purposes, provided the output is sufficient and properly controlled and directed.

**Experimental Studies**

One of the first published reports on the effects of microwaves on living tissues comes from the Mayo Clinic.<sup>10</sup> The results of these studies on dogs indi-

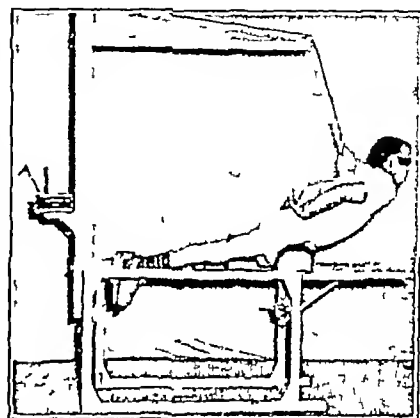


FIGURE 1 Exercise for Strengthening Neck Back Muscles. Hyperextension is made possible by counterbalance (A) in addition to the patient's maximum muscle power.

cated that microwaves were an effective heating agent. Rises of cutaneous temperature between 3 and 5 degrees were accomplished in twenty minutes with moderate output. Corresponding rises in subcutaneous and muscular tissue were also observed. Measurements of circulation were made with a bubble-flow meter that indicated increased venous return from the heated extremities. No unusual effects were observed other than those to be expected from the corresponding rises in temperatures of the tissues.

The Council on Physical Medicine has also investigated the microtherm generator produced by the Raytheon Manufacturing Company and has placed it in its list of accepted devices.<sup>11</sup> In experiments reported on human volunteers with measurements of deep-muscle temperatures it was found that increases to 103.5 to 105°F were obtained. It was noted that the sensation of cutaneous warmth was less than that usually expected by other means of



heating to a similar degree and that, for a given degree of cutaneous irritation, the rise in deeper tissue temperatures by microwaves was much greater than that produced by radiant heat

I have used an early model of the Raytheon microtherm\* over a period of a year. It has been utilized for heating purposes in a variety of conditions in the ordinary practice of physical medicine, including subdeltoid bursitis, radial humeral bursitis, non-suppurative tendinitis, muscle strain and contusion, and sinusitis. The usual technic of application included exposure for twenty minutes, which resulted in comfortable warming reported by the patient and increase of cutaneous temperature with mild erythema. Patients were warned about the sensation to be expected and were told to report undue warmth as with any heat treatment. No cases of blistering, burning or untoward effects were reported. An occasional patient felt increased discomfort in an acute bursitis in no wise different from that often resulting from short-wave diathermy. The results obtained are of no statistical significance, but from this period of clinical observation it is believed that this is a safe and effective means of supplying heat

\*Kindly supplied by the Raytheon Manufacturing Company, Waltham

to a localized area when employed with similar precautions applying to the use of diathermy. The opportunity to see the skin at all times during treatment is a technical advantage in avoiding excessive heating. This new electronic development appears to be a worthy addition to the therapeutic armamentarium of physical medicine. Further physiologic and clinical studies are indicated.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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#### CASE 34181

##### PRESENTATION OF CASE

A twenty-year-old housewife was admitted to the hospital complaining of lassitude and a movable lump in the abdomen.

Two years before admission the patient became pregnant and had a normal prenatal course for the first six months. At that time while at rest she had an episode of sudden severe pain low in the lumbar region, without any radiation and lasting twenty minutes. There was no dysuria, passage of stool or pain in the lower abdomen or genital region. At one other time during pregnancy she was said to have passed bloody urine. However, she had no urinalysis during pregnancy. She had pruritus vulvae and burning on urination during pregnancy. After parturition she had dizziness, which was cured by glasses. She had felt complete

lack of energy and had liver injections without effect. She ate heavily but could gain no weight (the weight was 125 pounds and during pregnancy it had been 142 pounds). Occasionally she had panicky feelings and spontaneous crying spells. She noted the presence of a slightly tender, movable lump in the right lower abdomen. She complained occasionally of mild shooting pain of right-obturator-nerve distribution. For two years during evening devotion she could not kneel and then lean forward because of pain in the midlumbar region. She had mild mucoid vaginal discharge.

There was no history of tremor, palpitation or heat intolerance. Her husband had "depressive spells," and they had been separated twice. The patient had a family history of diabetes. Six members of her family had "stiffening and fixation of the lower spine."

Examination revealed a pale, well developed, well nourished woman. There was a precordial systolic thrill and a Grade III systolic murmur best heard at the apex. There was tenderness over the right costovertebral angle and a tender, firm, 3-cm. mass in the right midportion of the abdomen. The mass was considered to be in the position of a ptotic kidney or caudate lobe of liver. It did not move with respiration. The right kidney was palpable and descended to the midportion of the abdomen. The left kidney was not felt. The cervix was lacerated, and the uterus retroflexed. There was slight adnexial tenderness. Reflexes in the legs were normal.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 85 diastolic.

Examination of the blood showed a hemoglobin of 38 gm and a white-cell count of 7800. The differential count was within normal limits. Urinalysis was negative. The lumbar spine was radiologically normal. An excretory urogram showed the kidneys to be normal in size, shape and position. The dye appeared promptly in both urinary tracts. There was no definite abnormality of calyces and pelves. The right ureter was somewhat kinked at its upper extremity, but this caused no obstruction. A film taken in the upright position showed both kidneys to descend about 5 cm. A barium enema revealed no intrinsic abnormality or external compression. An ill defined shadow was noted on the right side of the abdomen below the right kidney partially obscuring the shadow of the right psoas muscle. Lateral films taken at another hospital showed the presence of a mass below the right kidney, displacing the ureter medially and anteriorly.

On the fifth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. RICHARD SCHATZKI\* It does not seem out of place to start with the x-ray films. We shall first look at the films taken at the other hospital, about two weeks prior to admission. The films with catheters in both ureters show the left ureter in approximately normal position and the right ureter to be displaced far medially and overlying the spine. The shadow of the left psoas muscle is clearly visible, the right is visible but not so well defined. I cannot see a definite soft-tissue mass. The right kidney is well outlined and appears normal in size and shape. After injection of dye through the catheters normal kidney pelves are seen on both sides. The right ureter still maintains its position over the spine even after the catheter has been withdrawn partially, its displacement starts at the ureteropelvic junction. The lateral film shows the kidney in normal position, but the ureter, starting at the ureteropelvic junction, seems to be displaced forward. The films taken at this hospital show again a normal appearing kidney. The shadow of the left psoas muscle is clearly outlined, the right is outlined a little more clearly than on the films taken elsewhere. On some of the films I think I can see something that looks like a mass below the kidney, but this is by no means definite. There is disturbingly little visible to suggest a mass. The intravenous pyelograms do not outline the ureters well enough to determine their position. The upper end of the ureter on the right side shows some displacement forward as on the outside films,

and we will therefore assume that the ureter had the same position as on the previous examination.

A barium enema was performed and was said to be completely normal, without displacement of the colon. It is difficult to make a statement of displacement of the intestines from films unless there are a number of them or the displacement is quite marked, and I hesitate to express an opinion about anything that is so vaguely seen, but on these films I have the impression that the ascending colon is slightly more to the right than usual. In both these films after evacuation the whole colon drops down normally, there is no fixation of the colon anywhere. Of interest is the lateral film that was taken apparently after evacuation of the enema, and the thing that impresses me is that there seems to be a difference in the size of the abdomen compared with the films taken approximately two weeks previously. I measured the distance from the anterior abdominal wall to the anterior aspect of the spine on both films, and it certainly is greater on the recent film. The patient apparently was a slender woman, and very slight changes in position of the patient may influence the measurable thickness of the abdomen. So I do not know that we are justified in taking this difference in size of the abdomen as a definite fact, otherwise, it would be extremely interesting. That is as far as we can go on the x-ray appearance.

What conclusions can be drawn from the evidence so far? The logical conclusion is that this patient had a mass in the retroperitoneal space on the right side, which displaced the right ureter forward and to the left. There are many lesions in the retroperitoneal space that can produce such a displacement. There are numerous benign tumors that may occur there, the most common one probably being a neurofibroma. Could this have been a neurofibroma? The location is consistent. The patient's history would certainly go with the diagnosis. The patient had one attack of severe pain, which is unusual. She had occasional pain in the distribution of the obturator nerve, which runs along the medial aspect of the psoas muscle in the region where the pathologic lesion appears to be. We do not see any defect in the spine. A neurofibroma anywhere near the spine, even originating from the spine, does not have to deform the spine, and certainly in the abdomen, where there is so much space for a tumor to grow, it would not cause pressure defects in the spine. There are a few disturbing features about the diagnosis of neurofibroma. The first is that I cannot see the tumor on the plain films — disturbing for a tumor of this size. The other disturbing feature is the fact that clinically the mass is described as being 3 cm in diameter. If what was felt clinically coincides with what we believe to be the lesion in these films, the mass should be larger than 3 cm. Of course it is possible that the clinical mass represented only a portion

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of the x-ray mass, which would go well with neurofibroma, since neurofibroma is often lobulated. Neurofibroma is still a good possibility.

What other retroperitoneal tumors may occur? There may have been a lipoma in the retroperitoneal tissue. That would explain nicely why we see so little of the tumor mass. On the other hand we do not see any radiolucency, such as one would expect from a lipoma in this location. Against lipoma is the fact that the mass was readily palpable by the patient. I would rather believe that that makes the diagnosis unlikely.

Another mass in the retroperitoneal region in that area could be a cyst originating from the kidney. Cysts may originate particularly from the lower pole of the kidney, and the kidney shadow may appear to be perfectly normal, if the cysts are pedunculated. A pedunculated cyst of the lower pole of the right kidney could produce this picture. Again, it is rather surprising that we do not see a definite mass on the plain film.

There are all kinds of other queer tumors that may occur in this location. It is an interesting embryologic region. The wolffian and müllerian ducts may leave cysts behind. There are occasional cysts of the ureter, ovarian cysts and so forth. I do not know how one can make a definite diagnosis of any of these lesions. There are other benign tumors that I am sure may occur.

We have of course the possibility of malignant tumors, metastatic cancer may occur retroperitoneally. We do not have to worry too much about this possibility since the lesion had not changed much in two years' time. I do not believe that we can rule out a slowly growing sarcoma, fibrosarcoma or neurofibrosarcoma—in other words, a tumor similar to the first tumor that I mentioned, neurofibroma, only its malignant variant.

Another tumor in this area is the teratoma. I would not try to make a diagnosis from the evidence at hand. Dermoid cyst belongs to the congenital ones that I have already mentioned.

Was this lesion necessarily a tumor? An abscess in the retroperitoneal space would produce the same displacement of the ureter. There is nothing in the history to suggest abscess. A hemorrhage into the retroperitoneal space could produce such a displacement. Again, there is nothing in the history to suggest that the patient had a hemorrhage, although I think it is possible for someone to have a hemorrhage without any dramatic clinical story to go with it. That would explain the displacement and would explain why we see so little of a soft-tissue mass. I do not believe that we can rule it out, but with the negative history it is definitely a long shot.

Is it necessary to suppose that what we see had anything to do with the patient's complaint—not the lassitude, but the lump? It is possible that what we see is a red herring and that the patient

had an additional mass in the peritoneal cavity—a tumor of the small bowel 3 cm in diameter. Displacement of the ureters may occur with other conditions than masses, as we have already said. The ureter may be pulled over by a scarring process or by loss of substance on the side to which the ureter is pulled. Again, we have nothing to suggest this course of events. It would be helpful to find something in the peritoneal cavity that would explain the free mobility of the mass. On the other hand, the free mobility was an observation of the patient, there was no statement by the doctor that the mass was movable. Some mobility is possible in retroperitoneal tumors. The normal pancreas and the normal kidney have definite mobility. Pedunculated tumors may have a good deal of mobility. You may remember a case taken up at one of these conferences in which the discussor was led astray by just this fact—a pancreatic cyst that was freely movable, which had caused the discussor to rule out a retroperitoneal mass.

We have not enough evidence on which to base the possibility of an intraperitoneal mass.

I shall make a diagnosis of retroperitoneal mass. I do not know its histology. I shall place neurofibroma first and question of cyst of the lower pole of the kidney second, but I know very well that I have no right to make a histologic diagnosis.

DR WILLIAM A. CLARK: Will Dr. Schatzki comment on whether or not the sacroiliac joints look normal? Much of the symptomatology might be explained on the basis of mild rheumatoid spondylitis.

DR SCHATZKI: I would call them normal.

DR RONALD C. SNIFFEN: Do you agree with Dr. Schatzki's reasoning, Dr. Wyman?

DR STANLEY M. WYMAN: I agree completely.

#### CLINICAL DIAGNOSIS

Retroperitoneal tumor

#### DR SCHATZKI'S DIAGNOSIS

Retroperitoneal mass

Neurofibroma?

Cyst of lower pole of kidney?

#### ANATOMICAL DIAGNOSIS

*Ganglioneuroma, retroperitoneal*

#### PATHOLOGICAL DISCUSSION

DR SNIFFEN: Dr. Dobyns, you took care of this patient? Will you tell us what you know about her?

DR BROWN M. DOBYNS: Operation was performed by Dr. Oliver Cope. The patient was sent in in the belief that she had a tumor, probably above the kidney. The mass that was felt was thought to be the kidney. The x-ray films (retrograde pyelograms) that you have seen did not accompany the patient when she arrived. After a number of days of study she was about ready to be discharged because of lack of positive evidence that could be obtained.

Then we sent for the x-ray films, thinking that the doctor's idea that there was something in the renal region might be confirmed. The displacement of the ureter was well demonstrated in the retrograde pyelograms. Exploration was accomplished through a right transverse abdominal incision. The ascending colon was pushed forward by a mass, which was exposed by reflecting the right colon and cecum medially. The mass had several long fingers of tissue that extended upward and posterior to the vena cava, wrapping around and adherent to it. At the upper end this extended almost behind the liver. There were several secondary masses about the size of a golf ball in the connective tissue immediately adjacent to the main tumor. The whole mass was dissected out from above downward. We tied off a number of small vessels leading from the tumor to the vena cava. The mass was found to arise on a pedicle that came through a small aperture in the psoas muscle. It came through at the level of the third lumbar vertebra. This aperture is the usual anatomic pathway of the sympathetic commissure. The tumor was not adherent to the anterior branches of the lumbar plexus. It had no obvious relation to the obturator nerve or the anterior femoral cutaneous nerve, and it was thought that the tumor arose from sympathetic-nerve tissue because the sympathetic trunk was not present after removal of the tumor. The tumor was thought to have been completely removed.

DR SNIFFEN Did you think that the neoplastic tissue had multiple points of origin or was a single lobulated tumor?

DR DOBYSN We believed when we removed the specimen that there was a moderate amount of freedom between the secondary tumor nodules and the main mass. They were close enough to the main mass to have had some continuity.

DR SNIFFEN The tumor that Dr Cope removed was a lobulated, encapsulated mass. Microscopical sections showed a dense background of nerve fibers in which ganglion cells were embedded. In short, the tumor was a ganglioneuroma. As you know, the ganglioneuroma is the most highly differentiated tumor arising from the anlage of the autonomic nervous system. Usually, it is found in the adrenal medulla or along the line of the paravertebral ganglions. Metastasis does not occur, but multiple tumors are not a rarity. In neuroblastomas, which are the undifferentiated tumors of the sympathetic anlage, one occasionally finds areas of differentiation into ganglioneuroma. I should think that the prognosis is excellent in this case.

#### CASE 34182

##### PRESENTATION OF CASE

The patient was a full-term baby girl born in the hospital after a normal labor of twelve hours by a para V mother.

The pregnancy was uneventful. The mother was sedated with seconal (0.3 gm), amytal (0.4 gm), and scopolamine (0.4 mg). The child was born with the cord around the neck. The body was pink, and the head blue. She was reported to have cried spontaneously. The birth weight was 6 pounds, 15 ounces, and the length was 20 inches.

The mother's third child had died shortly after birth of atelectasis.

The baby was put in an incubator and given continuous oxygen because the color was dusky. Seven hours after birth she seemed to have some difficulty in breathing. Suctioning of mucus resulted in improvement for the next four hours. At that time, eleven hours after birth, the baby, who was being observed by the nurses frequently, was found to be blue and not breathing. Suctioning of mucus and artificial respiration with oxygen by nasal catheter were carried out by the nurse and doctors who responded to an emergency call. At that time the heart rate was 50 per minute. After a few minutes the baby started to breathe, with gasping respirations, and the color improved. The heart rate likewise improved. Though the chest did not appear fully expanded, auscultation indicated satisfactory aeration. During the next few hours the baby did fairly well with nasal oxygen, but the respirations remained somewhat irregular, with intervals of apnea. A second episode of respiratory standstill and cyanosis occurred approximately six hours later. During the next two days the baby was kept in oxygen in an incubator. The color was fair, but the respirations continued irregular at times. The heart sounds were of good quality. The lungs were clear. The fontanelle was not full. There were no convulsions. Feedings were attempted, but the baby did not swallow and gavage feedings were instituted. The baby expired on the fourth day of life.

##### DIFFERENTIAL DIAGNOSIS

DR RALPH A ROSS In consideration of a problem such as this, we are faced with two large groups of malformations or diseases: congenital malformations and those due to trauma during or preceding delivery or to chemical trauma from oversedation. Also, I think that we should mention, particularly because of the history of previous neonatal death in the family, transplacental sensitization producing erythroblastosis, and such esoteric infections as toxoplasmosis, which might appear during the first two or three days of life. However, there is no evidence in the subsequent course to suggest such conditions.

There are many congenital lesions that might be considered. There is a possibility of respiratory obstruction due to a lesion in the respiratory tract, such as tracheoesophageal fistula. The fact that the baby could be gavage fed with ease, rules out that possibility. A diaphragmatic hernia could

have caused the repeated spells of cyanosis. We have no evidence, however, to support that diagnosis. Cardiovascular anomalies, particularly severe lesions of the heart such as transposition of the great vessels, are frequently associated with an amazing degree of oxygenation of the peripheral blood over a period of days, and at post-mortem examination it is impossible to understand how the baby could have survived at all. We have, however, no way of determining the possibility of congenital cardiac lesions from the information at hand.

Trauma due possibly to oversedation with one of the narcotics or large doses of barbiturates, heavy intoxication with depression of the baby's centers can be a cause of this picture. However, the evidence given does not indicate that cause. Gross trauma due to the forces of labor or to the force exerted during delivery may cause hemorrhage into the subarachnoid or subdural space or from the venous sinuses subtentorially. Usually they are associated with more dramatic signs and a different course, and signs of increased intracranial pressure are commonly found. Asphyxia due to interference with the blood supply during the force of labor, because of placenta praevia, premature separation of the placenta, of which we have no evidence in this case, or pressure on the cord interfering with the baby's blood supply may very well be the cause of severe damage to the general system, with resulting petechial hemorrhages throughout many organs of the body. The brain substance itself, being more susceptible to anoxic injury, is the organ that shows most symptoms. This is borne out in the present case by the abolition of the swallowing reflex. Aspiration of amniotic fluid or mucus may be due to asphyxia, it may occur in the course of labor, and may be the cause of respiratory obstruction following delivery. Atelectasis of the lungs may be due to obstruction of the bronchioles or to inability of the baby to institute adequate respiratory motions. I think it is accepted that atelectasis is secondary, not primary, in a case of cyanosis. In the present case we have the evidence of the cord about the neck, with sufficient pressure on it to produce cyanosis of the superficial skin of the head at birth, without any cyanosis below the pressure point around the neck. We have evidence of general involvement of the central nervous system, with irregular respirations, the inability to take food and the abolition of the swallowing reflex. There were no

signs or evidence of any increased intracranial pressure. We have no laboratory data to help us, owing to the fact, I assume, that the infant's condition was so precarious that any such measures as x-ray study of the chest or examination of the spinal fluid were contraindicated by that condition.

My diagnoses, therefore, are asphyxia, with diffuse petechial hemorrhages, atelectasis secondary to those, and probably some aspiration pneumonia.

#### CLINICAL DIAGNOSES

Asphyxia  
Cerebral hemorrhage, multiple

#### DR. ROSS'S DIAGNOSES

Asphyxia  
Diffuse petechial hemorrhage in brain substance.  
Atelectasis

#### ANATOMICAL DIAGNOSES

*Aspiration of amniotic fluid, massive  
Thrombosis of superior longitudinal sinus*

#### PATHOLOGICAL DISCUSSION

DR. CHARLES S. KUBIK. I shall tell you about the findings in the brain, and Dr. Sniffen will give you the other findings. There was a thrombus in the posterior part of the superior longitudinal sinus. Some of the cerebral veins entering the sinus on the right side were greatly distended, whereas those on the left were not, and it was thought that these engorged veins were also thrombosed. There was considerable hemorrhagic extravasation in the dura and falx in the region of the superior longitudinal sinus. There were no hemorrhages within the substance of the brain or the brain stem, which on gross examination were not definitely abnormal.

We have microscopical sections of practically all parts of the brain, the brain stem and the cerebellum. It is very difficult to tell even now whether the superior longitudinal sinus and veins in question contained ante-mortem thrombi or post-mortem clots. We thought that they were probably thrombi, though very recent ones, with no reaction of the intima or the adjacent hemorrhagic dura, and certainly less than four or even two days old. It is, therefore, unlikely that these findings account to any large extent for the symptoms that were observed. The brain, mid-brain, pons and medulla were not remarkable.

DR ALLAN M BUTLER That means that microscopically you found no evidence of anoxia of the brain cells?

DR KUBIK Nothing that seemed significant.

DR BUTLER No evidence of petechial hemorrhage?

DR KUBIK Certainly nothing striking. Small hemorrhages within the substance of the brain are not at all uncommon as a terminal event in cases in which there has been serious respiratory difficulty.

DR ROSS The episodes of cyanosis that were observed after birth may have been sufficient to cause some degree of petechial hemorrhage.

DR KUBIK They may have. Anoxia may be of a degree to cause severe disturbance of cerebral function without producing any characteristic histopathological changes. Perhaps Dr Sniffen can throw further light on the situation.

DR RONALD C SNIFFEN The gross findings in the viscera were unimpressive. There was obvious collapse of both lungs, and the liver was slightly pale. Microscopically, there proved to be a serious change in the lungs in the form of massive inhalation of amniotic fluid, which was identified by the presence of the cells of the vernix caseosa. The fluid had reached and obstructed the respiratory bronchioles and sometimes the alveolar ducts and consequently the alveoli were not aerated. A hyaline membrane lined many of the bronchioles. The formation of the hyaline membrane is presumed to have been the result of exaggerated respiratory effort with margination of the protein precipitate within the air ducts. The liver showed quite marked fatty change, and there was a nephrosis that involved the proximal convoluted tubules. Both these changes are seen in anoxia.

DR KUBIK Would the changes in the lung account for the difficulty in respiration?

DR SNIFFEN I should think so. There was a massive aspiration, with unexpanded lung beyond the obstruction.

DR BUTLER I should think that the findings suggest clearly that the baby had intrauterine anoxia with accentuation of respirations and an undue aspiration of amniotic fluid and later on suffered further anoxia due to faulty functioning of the respiratory center as a result of the first intrauterine anoxia.

DR KUBIK I might say that it is difficult to evaluate recent nerve-cell changes in infants. Judged by standards that apply in adults the cells look diseased in almost every case. In this case it may be said that there was no actual loss of nerve cells and no findings that would justify a diagnosis of anoxia. That would have to be made on the basis of the clinical manifestations.

DR BUTLER How long is the period before such changes result in necrosis?

DR KUBIK In localized lesions resulting from arterial occlusion in adults there are well defined and distinct changes within fifteen hours and probably less. They would be more difficult to recognize in a diffuse process and against a background of terminal changes.

DR ROSS Why should the infant have had loss of swallowing reflex? The post-mortem findings do not explain it.

DR KUBIK There may be serious derangement of function in a nervous structure that cannot be recognized histologically.

DR BUTLER The baby's respirations were typical of the respiration that results from anoxic damage to the respiratory center.

DR KUBIK In our experience with human beings changes that we can recognize do not occur unless there has been loss of consciousness. Even then remarkably little may be found in some cases. In a case of carbon monoxide poisoning the patient had been unconscious for a number of hours and then lived for several days, finally dying of a pulmonary embolus. There were two small patches of degeneration, and nothing definitely abnormal in the rest of the brain.

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## THE LABORER AND HIS HIRE

THE task that faces the organized profession of medicine, the hospitals, hospital and medical service organizations and Government itself in determining the destiny of medical care constitutes one of the uppermost problems of the day. So great a cloud of witnesses is involved in any discussion of the problem that it is difficult to see clearly the issues involved and place them in their proper relation to one another.

Perhaps not of paramount importance but nevertheless particularly vexing have been the difficulties encountered as a result of Blue Cross payment of certain professional services rendered within hospitals and the relation between hospitals and staff physicians in certain branches of medicine. The

criticism has been made by these staff physicians, — anesthesiologists, pathologists and roentgenologists in particular, — who may be on full-time or part-time salaries, that employing hospitals have made a profit on their salaries and that Blue Cross, by arbitrarily including their services in its coverage, has classified the product of their training and experience as a hospital rather than a professional service.

They have thus been classed, it appears from their contention, with the clerks of a store or the employees of an industry from whose earnings a legitimate profit might be expected.

In an attempt to evaluate any grievance that any party may have, the purposes of professional organization should be clearly defined. It may be assumed that the first object of all medical organization is to provide the patient with the best possible care. A second legitimate object is to assure for the physician a decent and dignified standing in his community and a living commensurate with his ability and its industrious employment.

It is admitted that Blue Cross has blundered, it is apparent also that some hospitals have erred in failing to establish proper relations between staff and administration. The mistake is common when businessmen, occupied chiefly with balance sheets, have jurisdiction over institutions that are staffed by professional men jealous of the ethics and etiquette of their profession. Even the physician turned director is too often found, at least in the eyes of his former colleagues, worshipping the golden calf instead of heeding the commandments written in stone.

A committee was appointed by the Council of the Massachusetts Medical Society in the spring of 1947 "to define hospital services and medical services and to establish the proper relations between physicians and hospitals." This committee, composed of representatives of the anesthesiologists, the pathologists and the roentgenologists, the Blue Cross, the Blue Shield, the Hospital Association and the Massachusetts Medical Society, labored long and faithfully during the hot and humid summer that ensued. It brought in a unanimous report that has so far been unimpeachable and that defined as medical hospital services those "other than ad-

ministrative, rendered by a registered physician directly to or in behalf of an individual patient for the obtaining and interpretation of data, including consultation and advice, for the diagnosis, treatment and prevention of disease."

These services, specifically, were defined as embracing "the general and special practice of medicine, surgery and obstetrics, and the practice of the related specialties including anesthesiology, physical medicine, radiology, pathology and clinical pathology."

A basic principle recommended in the report was that each department (so far as possible) be self-supporting and that *neither the hospital nor the physician rendering the service should exploit the patient or each other*. The basis of financial arrangement, however, might be salary, commission, fees or any other method that would best meet the local situation.

Certain questions are not easily answered. Is a nurse anesthetist, operating under a doctor's orders, acting as his agent in a nurse's capacity or is she engaged in the practice of medicine? The point is open to debate. May a chemist, conducting his own clinical laboratory, perform an analysis and report the result to the physician submitting the material, if he does not presume to make a diagnosis? The organized pathologists believe not, but here, again, there is room for disagreement.

So long as organized medicine uses its organization for the benefit of the patient and the improvement of its own standards and public relations, well and good. If, however, its collective power should be used, as could easily happen, to protect its members against reasonable, honest and decent competition even from without the profession, it is treading dangerously close to the less attractive paths of trade unionism.

If the profession of medicine, blinded by its cloud of witnesses, closes its eyes to the fact that there are at least two reasonable sides to nearly any argument, it is simply blocking the very progress within its ranks that it is most desirous of promoting.

*Status quo* is but the eye of the hurricane and cannot prevail for long. Change is inherent in all human undertakings. The wrong of today may be the right of tomorrow. When the people of a nation have had

their minds made up, either by themselves or by some accepted agency they usually get eventually what they want or what they have been persuaded to think they want.

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## ARMY MEDICAL RESEARCH

WAR is no longer characterized by small battles between professional armies for limited objectives. Whole populations are now involved, and the stake is nothing less than national survival. Indeed, the survival of a civilization may well be at stake in some future conflict. This broader concept of war vastly increases the responsibilities of the physician. It will no longer be enough for him to relieve the fighting troops of their sick and wounded or give medical care to the civilian population. He must do these things in time of war by all existing means, but in time of peace he must work to improve known methods and to discover methods never known before.

A recent address by Lieutenant Colonel Alfred P. Thom, M.C., chief of the Army Medical Research and Development Board, throws further light on this subject. It is good to know that the medical departments of the armed forces are keenly aware of the importance of basic research in the production of discoveries leading to major scientific advances, without which applied research alone would often be sterile. To give an idea of what the medical man is up against, a few of the most urgent problems are cited as examples: development of new physical and mental standards for the most efficient use of manpower, development of principles and psychiatric techniques to prevent psychiatric casualties in war, prevention and care of casualties due to or complicated by radiation sickness and radiation burns, cold-weather operations, including preselection of personnel for Arctic service, prevention and treatment of injuries due to cold and evacuation aspects of Arctic warfare, bacterial warfare—discovery and development of defensive measures against all known and suspected disease agents, and improvements in traumatic surgery, in control of common disabling diseases, in antibiotics and in techniques of immunization.



When it is remembered that a future war may make no distinction between combatants and non-combatants, the figures for the Army in the last war will give an idea of what the magnitude of the medical problem may be. Between January 1, 1942, and August 31, 1945, approximately 17,000,000 men were hospitalized, and 773,000 more men were required, directly or indirectly, to give them medical care. Thus with 10,000,000 men mobilized, at least 1 out of 10 was out of action each day either as a patient or as required for patient care. This was with the best health, disease and injury treatment record of any army in history. It is anticipated that, with widespread use of atomic and other new weapons in a future war, a much greater proportion of personnel and resources will have to be used for patient care, and the proportion of sick and injured may be much higher. How much higher the actual figure could be is suggested by the present population figure of 145,000,000. One other figure — also in the millions — is of immediate interest, and that is the annual budget of the Army Medical Research Program. It is just over \$3,000,000.

Colonel Thom's closing words need no comment or elaboration.

Every medical graduate should make it his business to be acquainted with the significance of sickness and injury in military campaigns and their possible influence on national survival, so that, if medical risks are taken, the advice given to those responsible for leadership will be such that the odds are carefully considered to give the best chances for success. In total war as never before experienced in the past, a superior, progressive army medical service and staff are fundamental requirements for winning a war. The effect on morale of inadequate care of sick and injured, as well as losses in manpower due to these causes, may be catastrophic. No citizen with medical training can consider himself a disinterested onlooker in medical problems involved in national defense. Your city may be the one chosen as a military target. We must have a superior, integrated, civil and armed force medical service if the nation is to survive. Every medical graduate must actively participate in this service and do his or her part.

## NEW ENGLAND DOCTOR AND HIS PUBLIC

THE Council of the New England State Medical Societies continues to perform one of its most important functions. Organized in 1945 "to bring about a closer co-operation between the State Medical societies in New England in the develop-

ment and maintenance of the highest standards in the conduct and administration of medicine, and in the furtherance of plans to improve the health of all the people in the New England States," it has added to this purpose the establishment of sound relations between the medical profession and the public.

On Sunday, March 7, 1948, despite winter and bad weather, approximately seventy-five Council members and other interested persons gathered at the Copley Plaza Hotel to engage in a discussion on *The New England Doctor and His Public*. Most of those present being physicians, "not snow nor rain . . . nor gloom of night" stayed them from the completion of this particular appointment.

Dr. Arthur H. Ruggles, of Providence, president of the Council, presided. Talks were given on the value of radio as a public-relations agency by James S. Powers, director of the Yankee Network Institute, on the doctor and his medical society as sources of news by Maurice Cronan, city editor of the *Hartford Courant*, and Gerald E. McLaughlin, managing editor of the *Rutland, Vermont, Daily Herald*, and on the doctor's role in community programs by Dr. Hugh R. Leavell, professor of public-health practice at Harvard University School of Public Health. These addresses were discussed by Dr. John F. Conlin, director of medical information and education of the Massachusetts Medical Society, James G. Burch, director of public relations of the Connecticut State Medical Society, and Dr. Robert O. Blood, former governor of New Hampshire.

The relations between the medical profession and the news-dispensing agencies are at present and have always been poor. The doctors, according to Mr. Powers, still dwell in their ivory tower of seclusion, still maintaining a public-be-damned attitude so far as the divulging of any news is concerned. This opinion was concurred in by the newspaper editors on the program, although definite signs of improvement are making themselves manifest — such as the very meeting at which these sentiments were expressed.

It is time for the mystery and magic in medicine to be finally and completely abolished. The public should be given the opportunity of learning about

medicine all that it can assimilate within the limits of its nonmedical education. The recent controversy over the Nolen-Miles Pound Bill has shown how sadly this information has been lacking.

At the same time the press and its public must realize that many of the confidences reposed in the doctor are in the nature of privileged communications and that he is in honor bound to respect them. They must realize that matters having to do with health and disease must be reported faithfully and interpreted accurately, and must be freed from sensationalism.

If the doctor is slow to expose himself to reprobation it is because he has sometimes been burned by it. There is no question that his public relations need improving, but the improvement must be on a mutual basis.

## PEDIATRICS

A RECRUIT is welcomed into the swelling ranks of medical journalism with the appearance of *Pediatrics*, the new official organ of the American Academy of Pediatrics. *Pediatrics*, as a journal owned by the Academy, replaces in its relation to that society *The Journal of Pediatrics* that had been published in the interest of the Academy under the proprietorship of the C. V. Mosby Company. The latter journal continues its independent course, with Dr. Borden S. Veeder, of St. Louis as editor.

The new journal, the first issue of which appeared in January, 1948, is edited for the Academy by Dr. Hugh McCulloch, of St. Louis, and a representative board of well known pediatricians. The first issue contains a Salute by Dr. Allan M. Butler, of Boston, the presidential address, given in December, 1947, by Dr. Lee Forrest Hill at the annual meeting of the American Academy of Pediatrics in Dallas, Texas, and a variety of scientific and clinical articles. A useful addition to the usual method of publication of papers is a summary of each in Spanish.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**HAUPTMANN**—Alfred Hauptmann, M.D. of Newton Center, died on April 5. He was in his sixty-seventh year.

Dr. Hauptmann received his degree from Universität Heidelberg Medizinische Fakultät, Baden, in 1905. He came to the United States in 1939. He was a member of the staff of the Boston Dispensary, Joseph H. Pratt Diagnostic Hospital, and was medical director of the Bosworth Hospital.

His widow and a daughter survive.

**SCHULTZ**—Philip E. Schultz, M.D. of West Newton died on April 3. He was in his thirty-eighth year.

Dr. Schultz received his degree from Creighton University School of Medicine, Omaha, Nebraska, in 1933. He was a member of the American Society of Anesthetists Incorporated.

His widow survives.

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATHS

**LADD**—Samuel T. Ladd, M.D., of Portsmouth died on March 27. He was in his seventy-second year.

Dr. Ladd received his degree from Dartmouth Medical School in 1900. He was a former president of the New Hampshire Medical Society and was a member of the New Hampshire Surgical Society.

Three sons survive.

**RIECHMOND**—Allen P. Richmond, M.D. of Hingham died on March 17. He was in his eighty-eighth year.

Dr. Richmond received his degree from Bellevue Hospital Medical College in 1889. He was a life member of the New Hampshire Medical Society.

A son and two daughters survive.

## MEDICOLEGAL ABSTRACT

**Hospitals**—Standard of care required in the operation of the hospital pharmacy. The conduct of the modern hospital requires the operation of many related activities in connection with the hospitalization of patients. Interesting questions arise regarding the standard of care in the operation, supervision and maintenance of such activities as pharmacies, cafeterias, x-ray rooms, orthopedic gymnasiums and special appliance shops. One case that sometimes arises is the accidental substitution of a dangerous medication for a similar appearing but harmless drug. A recent Connecticut case involved such a problem.

A hospital maintained a pharmacy in the basement consisting of a workroom and a separate supply room. Boric acid and dextrose, which look alike, were purchased from the same concern in containers of similar cylindrical size and shape. A cylinder of each was kept on the floor of the pharmacy proper separated from each other by about four feet. The only distinguishing marks on the cylinders were the names of the medications and the additional words in small type on the boric acid container "for ex-

ternal use only" Boric acid is a poison and may be fatal to newborn babies if taken internally

Under hospital routine newborn infants were given a feeding of 5 per cent dextrose solution. On this occasion the maternity ward sent the dextrose bottle to the pharmacy to be refilled, and it was filled with boric acid, whose use in the formula resulted in the death of five babies and in injuries to a sixth. Since the hospital employed a registered pharmacist and there was apparently no negligence in his selection, it was not liable for any negligence of the pharmacist under the charitable immunity rule that prevails in Connecticut. The plaintiff, the administrator of the estate of one of the deceased babies, sought to recover, therefore, on the grounds that the hospital itself was negligent in failing to provide proper facilities, safeguards and surroundings in the pharmacy. The hospital, on the other hand, argued that it had established its pharmacy in accordance with standard practice, so that if there were any negligence involved in this respect, it was negligence on the part of the pharmacist to whom the hospital had properly delegated the job of running the pharmacy. The issue, therefore, was not whether the pharmacist or some other employee was negligent in using the wrong bottle, but whether the use of the wrong bottle resulted from a violation by the hospital management itself of a duty, which it could not delegate to subordinates, to provide certain safeguards against such mistakes in the operation of its pharmacy.

The trial court instructed the jury that certain duties were duties of the hospital and could not be delegated. In describing the extent of these non-delegable duties, the trial court said

This includes the duty to make provision for the inspection and use of all drugs, food, equipment, and appliances, and the report of anything unusual, uncommon or serious if, and insofar as, and to the extent that you find the making of such provision is involved in its corporate function of exercising reasonable care, in view of the functions of the hospital, and the dangers reasonably to be anticipated in their performance.

The jury returned a verdict for the plaintiff, but on appeal it was set aside and a new trial ordered. The judge's instruction to the jury was described as "entirely too broad a statement because it made the most trivial duties in connection with the running of the hospital non-delegable and possible bases of liability. If applied, it would practically eliminate the doctrine of charitable immunity of a hospital."

The court further stated

The trial court should not have submitted the question whether defendant failed to provide proper facilities and safeguards in the pharmacy to the jury. All of the evidence was to the effect that the pharmacy was set up in accordance with standard practice, and there was no evidence to the contrary. No written rules for its conduct had been prescribed, and there was no evidence that standard practice required this or that their existence would have changed the situation. The motion to set aside the verdict should have been granted.

In view of this conclusion, there is little in the appeal from the judgment which requires mention. The foregoing discussion negatives the claim of the defendant that charitable immunity protects a hospital even against true corporate negligence.

True corporate negligence has been defined by the Connecticut court in another case (*Evans v. Lawrence and Memorial Hospitals*, 50 Atl. 2d 443, 1946) as negligence on the part of the board of trustees acting as a board, or on the part of the executive committee of the hospital acting as such a committee within the scope of its authority. Such negligence ordinarily is in the selection of doctors, servants or employees and is a basis for liability in a number of states besides Connecticut.

This decision turns on the extent of the doctrine of charitable immunity in the particular state. In Massachusetts, on similar facts in the case of *Roosen v. Peter Bent Brigham Hospital* (235 Mass. 66) the substitution of corrosive sublimate for epsom salts—drugs that closely resemble each other and were kept in near proximity to each other in the pharmacy—and on an action to hold the hospital for corporate negligence in the selection of servants, the court stated

If a hospital is to be held responsible for negligent treatment of patients, there seems to us to be no sound ground for distinction between the negligence of the managers of the hospital and the negligence of subordinate servants as a basis for liability. A sound ground for distinction between exoneration from liability for the negligence of managers and that of subordinate servants seems equally wanting. Since it is settled that there is no liability for negligence of the latter, it must follow that there is none for that of the former. The inevitable result of our own decisions is to relieve a hospital from liability for negligence of the managers in selecting incompetent subordinate agents, as well as for the negligence of such subordinate agents selected with care.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The May schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows

CLINIC	DATE	CLINIC CONSULTANT
Salem	May 3	Paul W. Hugenberger
Lowell	May 7	Albert H. Brewster
Gardner	May 11	Carter R. Rowe
Haverhill	May 12	William T. Green
Brockton	May 13	George W. Van Gorder
Springfield	May 18	Garry deN. Hough, Jr.
Pittsfield	May 19	Frank A. Slowick
Worcester	May 21	John W. O'Meara
Fall River	May 24	David S. Grice
Hyannis	May 27	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

## MISCELLANY

## BOSTON CITY HOSPITAL ALUMNI ASSOCIATION

The Boston City Hospital Alumni Association held its sixteenth annual reunion and dinner at the Harvard Club of Boston on April 24.

The conspicuous event of the evening was the presentation of the newly established Major General Leonard Wood award to Dr. Elliott P. Joslin. This award will be given to distinguished members of the Association who have achieved fame in medicine or surgery.

## CORRESPONDENCE

## RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held April 8, it was voted to restore the registration to practice medicine in this Commonwealth to Dr. Mary E. Bolger formerly of Worcester.

H. QUINBY GALLUPE, M.D. Secretary  
Board of Registration in Medicine

State House  
Boston

## SERUM JAUNDICE

To the Editor: In the March 25 issue of the *Journal*, under the heading of Idiopathic Hyperlipemia Hopgood cited the history of a twenty six year-old man with this condition. The patient was first admitted to the hospital on December 11, 1946 when various tests were performed among them being blood chemical determinations. He was discharged and was readmitted two months later for further study, but immediately started to run the classic course of hepatitis. The author states that the jaundice is believed to have been a simple infectious hepatitis.

The course of events that occurred in the case reported has subsequently been repeated many times. In the past year or two it has been increasingly distressing on acute ward services where many venipunctures or injections are given, to have the patients return in two or three months with hepatitis. Although no blood or blood products are administered in these cases their incubation periods justify their inclusion in the category of homologous serum jaundice. The virus is transmitted from an asymptomatic carrier or an active case to the hospital patient under investigation by the agency of improperly cleaned syringes or needles. A drop of serum remaining in a syringe is all that is necessary to infect a new victim. Because of this situation every puncture of a patient's skin whether for blood sugar, white-cell count or to introduce penicillin poses a potential threat to an already sick person unless certain precautions are taken.

Individual syringes and needles should be used whenever practicable. Certainly in cases of infectious hepatitis this is most desirable. If this measure cannot be carried out, all syringes should be thoroughly washed and needles sterilized and rinsed. For the time being autoclaving remains the preferred method of sterilization.

These precautions are simple and well worth the trouble in view of the increasing incidence of "hospital hepatitis".

MARTIN C. ROSENTHAL, M.D.

115 Central Park West New York 23 New York

*The Thematic Apperception Test: The theory and technique of interpretation* By Silvan S. Tomkins, Ph.D. research associate College Entrance Examination Board and visiting lecturer in clinical psychology, Princeton University. With the collaboration of Elizabeth J. Tomkins, B.A. 8° cloth, 297 pp. New York: Grune and Stratton, 1947. \$5.00.

*Handbook of Psychiatry* By Winfred Overholser, M.D., Sc.D., superintendent, St. Elizabeth's Hospital, and professor of psychiatry, George Washington University School of Medicine, Washington, D.C., and Winifred V. Richmond, A.M., Ph.D. 8° cloth, 252 pp. Philadelphia: J.B. Lippincott Company, 1947. \$4.00.

*Diagnosis in Daily Practice: An office routine based on the incidence of various diseases* By Benjamin V. White, M.D., assistant clinical professor of medicine, Yale University School of Medicine, consultant in gastroenterology, Veterans Administration Hospital, Newington Conn. branch section chief in gastroenterology (New England) Veterans Administration and assistant visiting physician and chief of Gastroenterologic Clinic, Hartford Hospital and Charles F. Geschickter, M.D., professor of pathology, Georgetown University School of Medicine, consultant in pathology, United States Naval Medical School, Bethesda, Maryland, consultant in pathology, Mt. Alto Veterans Administration Hospital, Washington, D.C., and pathologist-in-chief, Gallinger Municipal Hospital, Washington, D.C. 8° cloth, 693 pp. with 360 illustrations and 104 tables. Philadelphia: J.B. Lippincott Company, 1947. \$15.00.

*Nutritional Disorders of the Nervous System* By John D. Spillane, B.Sc., M.D. (Wales), M.R.C.P. (London), assistant physician and neurologist, Cardiff Royal Infirmary. With a foreword by George Riddoch, M.D., F.R.C.P. physician to the London Hospital and to the National Hospital for Nervous Diseases, Queen Square, London. 8° cloth, 280 pp., with 103 illustrations. Baltimore: The Williams and Wilkins Company, 1947. \$5.00.

*Stereoscopic Atlas of Neuroanatomy* By H. S. Rubinstein, M.D., Ph.D. director, Alfred Ullman Laboratory for Neuropsychiatric Research, Sinai Hospital, Baltimore, and C. L. Davis, M.D., professor of anatomy, School of Medicine, University of Maryland. 8° paper, 19 pp. with 43 plates. New York: Grune and Stratton, 1947. \$10.00.

*Trichomonas Vaginalis and Trichomoniasis* By Ray E. Trussell, M.D. associate in hygiene and preventive medicine. With an introduction by E. D. Plann, M.D., professor of obstetrics and gynecology, State University of Iowa College of Medicine. 8° cloth, 277 pp., with 19 illustrations and 16 tables. Springfield, Illinois: Charles C. Thomas, 1947. \$6.00.

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*Diseases of the Heart and Circulation* By Albert A. F. Peel, M.A. D. (Oxon), F.R.F.P.S. (G.) professor of medicine, Anderson College of Medicine, Glasgow, and assistant physician, Victoria Infirmary, Glasgow. Oxford Medical Publications. 8° cloth, 398 pp., with 61 illustrations. London: Oxford University Press, 1947. \$9.75.

*Calcific Disease of the Aortic Valve* By Howard T. Karsner, M.D., and Simon Kolesky, M.D. Institute of Pathology, Western Reserve University and the University Hospitals of Cleveland. 8° cloth, 107 pp. Philadelphia: J.B. Lippincott Company, 1947. \$5.00.

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*Office Treatment of the Eye* By Elias Selinger, M.D. attending ophthalmologist, Mt. Sinai, Cook County and Michael Reese Hospitals. 8° cloth, 542 pp., with 67 illustrations. Chicago: The Year Book Publishers Incorporated. \$7.75.

ternal use only" Boric acid is a poison and may be fatal to newborn babies if taken internally

Under hospital routine newborn infants were given a feeding of 5 per cent dextrose solution. On this occasion the maternity ward sent the dextrose bottle to the pharmacy to be refilled, and it was filled with boric acid, whose use in the formula resulted in the death of five babies and in injuries to a sixth. Since the hospital employed a registered pharmacist and there was apparently no negligence in his selection, it was not liable for any negligence of the pharmacist under the charitable immunity rule that prevails in Connecticut. The plaintiff, the administrator of the estate of one of the deceased babies, sought to recover, therefore, on the grounds that the hospital itself was negligent in failing to provide proper facilities, safeguards and surroundings in the pharmacy. The hospital, on the other hand, argued that it had established its pharmacy in accordance with standard practice, so that if there were any negligence involved in this respect, it was negligence on the part of the pharmacist to whom the hospital had properly delegated the job of running the pharmacy. The issue, therefore, was not whether the pharmacist or some other employee was negligent in using the wrong bottle, but whether the use of the wrong bottle resulted from a violation by the hospital management itself of a duty, which it could not delegate to subordinates, to provide certain safeguards against such mistakes in the operation of its pharmacy.

The trial court instructed the jury that certain duties were duties of the hospital and could not be delegated. In describing the extent of these non-delegable duties, the trial court said:

This includes the duty to make provision for the inspection and use of all drugs, food, equipment, and appliances, and the report of anything unusual, uncommon or serious if, and insofar as, and to the extent that you find the making of such provision is involved in its corporate function of exercising reasonable care, in view of the functions of the hospital, and the dangers reasonably to be anticipated in their performance.

The jury returned a verdict for the plaintiff, but on appeal it was set aside and a new trial ordered. The judge's instruction to the jury was described as "entirely too broad a statement because it made the most trivial duties in connection with the running of the hospital non-delegable and possible bases of liability. If applied, it would practically eliminate the doctrine of charitable immunity of a hospital."

The court further stated:

The trial court should not have submitted the question whether defendant failed to provide proper facilities and safeguards in the pharmacy to the jury. All of the evidence was to the effect that the pharmacy was set up in accordance with standard practice, and there was no evidence to the contrary. No written rules for its conduct had been prescribed, and there was no evidence that standard practice required this or that their existence would have changed the situation. The motion to set aside the verdict should have been granted.

In view of this conclusion, there is little in the appeal from the judgment which requires mention. The foregoing discussion negatives the claim of the defendant that charitable immunity protects a hospital even against true corporate negligence.

True corporate negligence has been defined by the Connecticut court in another case (*Ernst v. Lawrence and Memorial Hospitals*, 50 Atl. 2d 443, 1946) as negligence on the part of the board of trustees acting as a board, or on the part of the executive committee of the hospital acting as such a committee within the scope of its authority. Such negligence ordinarily is in the selection of doctors, servants or employees and is a basis for liability in a number of states besides Connecticut.

This decision turns on the extent of the doctrine of charitable immunity in the particular state. In Massachusetts, on similar facts in the case of *Roosen v. Peter Bent Brigham Hospital* (235 Mass. 66) the substitution of corrosive sublimate for epsom salts—drugs that closely resemble each other and were kept in near proximity to each other in the pharmacy—and on an action to hold the hospital for corporate negligence in the selection of servants, the court stated:

If a hospital is to be held responsible for negligent treatment of patients, there seems to us to be no sound ground for distinction between the negligence of the managers of the hospital and the negligence of subordinate servants as a basis for liability. A sound ground for distinction between exoneration from liability for the negligence of managers and that of subordinate servants seems equally wanting. Since it is settled that there is no liability for negligence of the latter, it must follow that there is none for that of the former. The inevitable result of our own decisions is to relieve a hospital from liability for negligence of the managers in selecting incompetent subordinate agents, as well as for the negligence of such subordinate agents selected with care.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The May schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Salem	May 3	Paul W. Hugenberger
Lowell	May 7	Albert H. Brewster
Gardner	May 11	Carter R. Rowe
Haverhill	May 12	William T. Green
Brockton	May 13	George W. Van Gorder
Springfield	May 18	Garry deN. Hough, Jr.
Pittsfield	May 19	Frank A. Slowick
Worcester	May 21	John W. O'Meara
Fall River	May 24	David S. Gnee
Hyannis	May 27	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

# MISCELLANY

## BOSTON CITY HOSPITAL ALUMNI ASSOCIATION

The Boston City Hospital Alumni Association held its sixteenth annual reunion and dinner at the Harvard Club of Boston on April 24.

The conspicuous event of the evening was the presentation of the newly established Major General Leonard Wood award to Dr Elliott P Joslin. This award will be given to distinguished members of the Association who have achieved fame in medicine or surgery.

# CORRESPONDENCE

## RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held April 8 it was voted to restore the registration to practice medicine in this Commonwealth to Dr Mary E. Bolger, formerly of Worcester.

H QUIMBY GALLUPE, M.D. Secretary  
Board of Registration in Medicine.

State House  
Boston

## SERUM JAUNDICE

To the Editor: In the March 25 issue of the *Journal* under the heading of "Idiopathic Hyperlipemia" Hopgood cited the history of a twenty-six year-old man with this condition. The patient was first admitted to the hospital on December 11, 1946 when various tests were performed among them being blood chemical determinations. He was discharged and was readmitted two months later for further study, but immediately started to run the classic course of hepatitis. The author states that the jaundice is believed to have been a simple infectious hepatitis.

The course of events that occurred in the case reported has subsequently been repeated many times. In the past year or two it has been increasingly distressing on active ward services where many venepunctures or injections are given, to have the patients return in two or three months with hepatitis. Although no blood or blood products are administered in these cases their incubation periods justify their inclusion in the category of homologous serum jaundice. The virus is transmitted from an asymptomatic carrier or an active case to the hospital patient under investigation by the agency of improperly cleaned syringes or needles. A drop of serum remaining in a syringe is all that is necessary to infect a new victim. Because of this situation every puncture of a patient's skin, whether for blood sugar, white-cell count or to introduce penicillin poses a potential threat to an already sick person unless certain precautions are taken.

Individual syringes and needles should be used whenever practicable certainly, in cases of infectious hepatitis this is most desirable. If this measure cannot be carried out, all syringes should be thoroughly washed and needles sterilized and rinsed. For the time being autoclaving remains the preferred method of sterilization.

These precautions are simple and well worth the trouble in view of the increasing incidence of hospital hepatitis.

MARTIN C ROSENTHAL, M.D.

115 Central Park West, New York 23 New York

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*The Thematic Apperception Test. The theory and technique of interpretation.* By Silvan S. Tomkins, Ph.D., research associate, College Entrance Examination Board, and visiting lecturer in clinical psychology, Princeton University. With the collaboration of Elizabeth J. Tomkins, B.A., 8°, cloth 297 pp. New York: Grune and Stratton 1947 \$5.00.

*Handbook of Psychiatry* By Winfred Overholser, M.D., Sc.D. superintendent, St. Elizabeths Hospital and professor of psychiatry, George Washington University School of Medicine, Washington D.C. and Winifred V. Richmond, A.M., Ph.D., 8°, cloth, 252 pp. Philadelphia: J.B. Lippincott Company, 1947 \$4.00.

*Diagnosis in Daily Practice. An office routine based on the incidence of various diseases.* By Benjamin V. White, M.D., assistant clinical professor of medicine, Yale University School of Medicine, consultant in gastroenterology, Veterans Administration Hospital, Newington, Conn., branch section chief in gastroenterology (New England) Veterans Administration, and assistant visiting physician and chief of Gastroenterologic Clinic, Hartford Hospital, and Charles F. Geschickter, M.D., professor of pathology, Georgetown University School of Medicine, consultant in pathology, United States Naval Medical School, Bethesda, Maryland, consultant in pathology, Mt. Alto Veterans Administration Hospital, Washington D.C., and pathologist-in-chief, Gallinger Municipal Hospital, Washington D.C., 8°, cloth 693 pp., with 360 illustrations and 104 tables. Philadelphia: J.B. Lippincott Company, 1947 \$15.00.

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*Calcific Disease of the Aortic Valve.* By Howard T. Kerner, M.D. and Simon Kolesky, M.D., Institute of Pathology, Western Reserve University and the University of Cleveland. 8°, cloth 107 pp. Philadelphia: J.B. Lippincott Company 1947 \$5.00.

*Biochemistry of Cancer* By Jesse P Greenstein, head biochemist and chairman, section on biochemistry, National Cancer Institute, National Institute of Health, United States Public Health Service, Bethesda, Maryland 8°, cloth, 389 pp, with 39 illustrations and 104 tables New York Academic Press, Inc, 1947 \$7 80

*The Psycho-analytical Approach to Juvenile Delinquency Theory case-studies treatment* By Kate Friedlander, M D (Berlin), L R C P, L R C S (Edin), D P M (London), Hon psychiatrist, Institute for the Scientific Treatment of Delinquency, and clinical director, West Sussex Child Guidance Service 8°, cloth, 296 pp New York International Universities Press, 1947 \$5 50

*The Oculorotary Muscles* By Richard G Scobee, M D, instructor in ophthalmology, Washington University School of Medicine, St. Louis 8°, cloth, 359 pp, with 112 illustrations St Louis The C V Mosby Company, 1947 \$8 00

*Blood Derivatives and Substitutes Preparation, storage, administration and clinical results including a discussion of shock, etiology, physiology, pathology and management* By Charles S White, M D, Sc D, chief of surgery, Doctors Hospital, consultant to Garfield Hospital, Providence Hospital, and Columbia Hospital, Washington, D C, and to U S Naval Hospital, Bethesda, Maryland, and Jacob J Weinstein, M D, associate in surgery, School of Medicine, George Washington University, associate in surgery at Gallinger Municipal Hospital and George Washington University Hospital, Washington, D C 8°, cloth, 484 pp, with 195 illustrations Baltimore Williams and Wilkins Company, 1947 \$7 50

*Medicine for Moderns The new science of psychosomatic medicine* By Frank G Slaughter, M D 8°, cloth, 246 pp New York Julian Messner, Inc, 1947 \$3 50

*Reading and Visual Fatigue* By Leonard Carmichael, Ph D, president, Tufts College, and director, Tufts Research Laboratory of Sensory Psychology and Physiology, and Walter F Dearborn, M D, Ph D, director, Psycho-Educational Clinic and professor of education, Harvard University 8°, cloth, 483 pp, with 103 illustrations and 6 tables Boston Houghton Mifflin Company, 1947 \$5 00

*The Echo* By Lila Van Saher 8°, cloth, 255 pp New York E P Dutton and Company, Incorporated, 1947 \$2 75

*Dermatology in General Practice* By Sigmund S Greenbaum, M D, professor of clinical dermatology and syphilology, University of Pennsylvania Graduate School of Medicine, dermatologist, Philadelphia General Hospital, Eagleville Sanatorium, Philadelphia Psychiatric Hospital, Bamberger Seashore Home, Atlantic City, Betty Bacharach Home, Atlantic City, Rush Hospital, and Camden General Hospital, and consultant dermatologist, Mt Sinai Hospital 4°, cloth, 889 pp, with 846 illustrations Philadelphia F. A Davis Company, 1947 \$12 00

*Clinical Neuro-Ophthalmology* By Frank B Walsh, M D, F R C (Ed), associate professor of ophthalmology, The Johns Hopkins University 4°, cloth, 1532 pp, with 384 illustrations Baltimore Williams and Wilkins Company, 1947 \$15 00

*Hodgkin's Disease and Allied Disorders* By Henry Jackson, Jr, M D, assistant professor of medicine, Harvard Medical School, and associate physician, Thorndike Memorial Laboratory, Boston City Hospital, and Frederic Parker, Jr, M D, associate professor of pathology, Harvard Medical School, and pathologist-in-chief, Boston City Hospital Oxford Medical Publications 4°, cloth, 177 pp, with 15 plates New York Oxford University Press, 1947 \$6 50

*Congenital Malformations of the Heart* By Helen B Taussig, M D, associate professor of pediatrics, Johns Hopkins University School of Medicine, and director of the Children's Cardiac Clinic at the Harriet Lane Home of the Johns Hopkins Hospital 4°, cloth, 618 pp, with 177 illustrations New York The Commonwealth Fund, 1947, \$10 00

*Practical Office Gynecology* By Karl J Karnaky, M.D., assistant professor of clinical gynecology, Baylor University College of Medicine, gynecologist to Jefferson Davis Hospital, Houston, Texas, and director of Menstrual Disorder Clinic, Jefferson Davis Hospital 4°, cloth, 261 pp, with 113 illustrations Springfield, Illinois Charles C Thomas, 1947 \$7 50

*Jaundice Its pathogenesis and differential diagnosis* By El R Movitt, M D, acting chief of medicine, Veterans Administration Hospital, Oakland, California 8°, cloth, 261 pp, with 22 illustrations and 34 tables New York Oxford University Press, 1947 \$6 50 Oxford Medical Publications

*Surgical Treatment of the Abdomen* Supervising editor, Frederic W Bancroft, M D Associate editor, Preston A Wade, M D, associate professor of clinical surgery, Cornell University Medical College, clinical professor of surgery, New York Medical College, attending surgeon, City Hospital of New York, and associate attending surgeon, New York Hospital 4°, cloth, 1026 pp, with 457 illustrations and 3 color plates Philadelphia J B Lippincott Company, 1947 \$18 00

*Textbook of Human Physiology* By William F Hamilton, Ph D, professor of physiology, University of Georgia School of Medicine 8°, cloth, 504 pp, with 121 illustrations Philadelphia F A Davis Company, 1947 \$6 00

*Transactions of the American Association of Genito-Urinary Surgeons* Fifty-seventh annual meeting held at Stock bridge, Massachusetts, June 20, 21 and 22, 1946 Volume XXXVIII 8°, paper, 305 pp Saint Paul The Bruce Publishing Company, 1947

## NOTICES

### ANNOUNCEMENT

Dr Samuel H Marder announces the removal of his office to 311 Commonwealth Avenue, Boston

### JOSEPH H PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a m

#### MEDICAL CONFERENCE PROGRAM

- Wednesday, May 5 — Neuro-anatomic Mechanisms Underlying Vertigo and Nausea Dr Benjamin Spector
- Friday, May 7 — Renal Tuberculosis Dr Roger C Graves
- Wednesday, May 12 — Pediatric Clinicopathological Conference. Drs James M Baty and H E MacMahon
- Friday, May 14 — Zinc Content of Whole Blood in Normal People and in Patients with Blood Dyscrasias Dr John G Gibson, 2nd
- Wednesday, May 19 — Human Heredity with Special Reference to Mediterranean Anemia Dr Isidore Ludwin
- Friday, May 21 — Problems Relating to Bacterial Resistance. Dr Tom Fite Paine, Jr
- Wednesday, May 26 — Non-Specific Urethritis Dr Lewis W Kane
- Friday, May 28 — Some Actions of Folic Acid Conjugates and Antagonists on Malignant Tumors Dr Sidney Farber

On Tuesday and Thursday mornings from 9 to 10 Dr S J Thannhauser will give medical clinics on hospital cases. On the second and fourth Friday afternoons of each month therapeutic conferences will be held from 2 to 4 with round

NOTICES (Concluded from page 648)

- SEPTEMBER 13-15 American Academy of Pediatrics, Olympic Hotel, Seattle, Washington  
 SEPTEMBER 20-23 American Hospital Association Page 310 Issue of February 26.  
 SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 Issue of January 29  
 OCTOBER 6-9 American Board of Ophthalmology Page 170 Issue of January 29  
 NOVEMBER 1-3 American Clinical and Climatological Association Page 582 Issue of April 15  
 NOVEMBER 6-12 American Public Health Association Page 420 Issue of March 18.  
 NOVEMBER 20-23 American Academy of Pediatrics, Annual Meeting, Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey  
 DECEMBER 7-9 Southern Surgical Association Annual Meeting, Page 343 Issue of April 8.

DISTRICT MEDICAL SOCIETIES

FRANKLIN

May 11 Annual Meeting Hotel Weldon Greenfield

MIDDLESEX EAST

May 12. Annual Meeting 6:45 p.m. Bear Hill Golf Cl b, Wakelee

WOKFOLK

May 1 Annual Meeting Hotel Kanmore Boston

PLYMOUTH

May 20 Lakeville Sanatorium, Lakeville.

SUFFOLK

- May 1 Spring Dinner  
 May 4 Annual Meeting  
 May 6. Censors Meeting

WORCESTER

May 12. Annual Meeting

# TUFTS COLLEGE MEDICAL SCHOOL

## Postgraduate Division

PRINCIPLES OF SURGICAL TECHNIQUE June 1 - July 10

Candidates must have had previous surgical training and experience. Laboratory work consisting of operations upon animals, is supplemented by lectures and illustrated demonstrations. Drs C Stuart Welch and Lewis S. Pilcher in charge. Tuition fee \$200. Enrollment limited to 30.

### Courses for the General Practitioner

RADIOLOGY May 12-14. A three-day full-time course in chest x-ray including roentgenologic interpretations of the heart and lungs in health and disease. Dr Alice Ettinger in charge. Tuition fee \$25

OPHTHALMOLOGY June 2-23 Monday Wednesday and Friday mornings. The commoner external eye diseases and their treatment are taught through demonstration of patients. Instruction is given in the proper use of the ophthalmoscope with interpretations of the normal fundus and fundus lesions in relation to general medicine. Dr Joseph Iperheimer in charge. Tuition fee \$75. Enrollment limited to 5. Ophthalmoscope required.

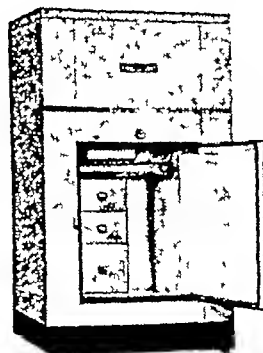
PEDIATRICS, June 1-12 This is a two-week full-time course in which problems both physical and mental, are discussed and demonstrated by pediatricians specializing in specific aspects of childhood disturbances. Dr Irving Silverman in charge. Tuition fee \$75

All courses may be taken under the G. I. Bill of Rights

For application forms and further information address

Director Postgraduate Teaching  
 Joseph H Pratt Diagnostic Hospital  
 30 Bonnet Street Boston 11 Mass

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Accepted for advertising in the Journal of the A.M.A.  
 WRITE FOR DESCRIPTIVE LITERATURE





## INTERNATIONAL CONGRESSES ON TROPICAL MEDICINE AND MALARIA

The fourth International Congresses on Tropical Medicine and Malaria and the first to be held since 1938 will convene in Washington, D. C., from May 10 to 18. The Congresses will be held under the auspices of the Department of State, and of over sixty nations to which invitations have been extended, thirty-three have already accepted and will send official delegations.

## MEDICAL VETERANS OF WORLD WAR II

An organizational meeting of physicians who served in World War II will be held at the Boston Medical Library on Thursday, May 13, at 8 00 p. m. The purpose of the proposed organization is to form a democratic group of physicians for the advance and protection of the medical profession in general and of the physician-veteran in particular.

Such an organization is particularly appropriate at the present critical time, and every physician who is a veteran of the recent war is urged to attend. Please notify friends who may be eligible.

Further information may be obtained from Kenneth A. Brown, M.D., 442 Walnut Street, Newtonville (Telephone Bigelow 4-0394).

## CHILDREN'S HOSPITAL ALUMNI ASSOCIATION

The annual meeting and dinner of The Children's Hospital Alumni Association will be held at the Hotel Berconshild, Brookline, on Wednesday, June 2, at 6 30 p. m. A short business meeting will be held, but the evening will be devoted mainly to social activities. Mr. Bradford Washburn will show colored films on Alaska.

Before the meeting a clinicopathological conference will be held in the amphitheater of the Peter Bent Brigham Hospital from 12 00 m. to 1 00 p. m., and a clinical meeting and presentation of cases will be conducted in the amphitheater of The Children's Hospital from 2 00 to 4 30 p. m.

## LASKER AWARD

The 1948 Lasker Award of \$1000 for outstanding service in mental hygiene will be presented for a recent significant contribution to the education of the physician in the psychologic aspects of the practice of medicine (by "physician" is specified the nonpsychiatric medical practitioner), it was recently announced. The work of the candidates for the award must have been accomplished or generally accepted during the past year or two. Presentation of the award will be made at the annual meeting of the National Committee for Mental Hygiene on November 3 and 4 in New York City.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 6

#### FRIDAY, MAY 7

- \*9 00-10 00 a. m. Renal Tuberculosis Dr. Roger C. Graves, Joseph H. Pratt Diagnostic Hospital
- 10 00 a. m. Annual Alumni Meeting Boston University School of Medicine
- \*10 00 a. m.-12 00 m. Medical Staff Rounds Peter Bent Brigham Hospital

#### MONDAY, MAY 10

- \*12 00 m. Clinicopathological Conference Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge

#### TUESDAY, MAY 11

- \*12 15-1 15 p. m. Clinicorontgenological Conference Peter Bent Brigham Hospital
- \*1 30-2 30 p. m. Pediatric Rounds Burnham Memorial Hospital for Children, Massachusetts General Hospital
- \*8 00 p. m. New England Society of Anesthesiologists Bigelow Amphitheater of the White Building, Massachusetts General Hospital
- 8 15 p. m. Harvard Medical Society Amphitheater of Building D, Harvard Medical School

#### WEDNESDAY, MAY 12

- \*9 00-10 00 a. m. Pediatric Clinicopathological Conference Drs. James M. Baty and H. E. MacMahon, Joseph H. Pratt Diagnostic Hospital
- \*12 00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital
- \*2 00-3 00 p. m. Combined Clinic by the Medical Surgical and Orthopedic Services, Amphitheater, Children's Hospital

- 5 15 p. m. Norfolk District Medical Society and Woman's Auxiliary, Hotel Kenmore, Boston
- 6 30 p. m. South Boston Medical Society Annual Dinner, Harvard Club of Boston

### \*Open to the medical profession

- APRIL 30 and MAY 1 American Gastro Enterological Association, Page 456, issue of March 25
- MAY 1 Suffolk District Medical Society Page 543, issue of April 8
- MAY 3 American Society for Clinical Investigation Page 456, issue of March 25
- MAY 3 and 4 Association of American Physicians Page 492, issue of April 1
- MAY 4 Suffolk District Medical Society Annual Meeting Page 562, issue of April 15
- MAY 4 and 5 Association of Military Surgeons of the United States Page 456, issue of March 25
- MAY 5 New England Obstetrical and Gynecological Society Page 611, issue of April 22
- MAY 5 Tufts Medical Alumni Lecture Page 647
- MAY 5-28 Joseph H. Pratt Diagnostic Hospital Medical Conference Program Page 646
- MAY 6 Suffolk Censors' Meeting Page 344, issue of March 4
- MAY 6-8 American Association for the Study of Gonorrhea Page 331, issue of July 31
- MAY 7 Boston University School of Medicine Alumni Association Page 647
- MAY 10-18 International Congresses on Tropical Medicine and Malaria Notice above
- MAY 11 Harvard Medical Society Page 647
- MAY 11 New England Society of Anesthesiologists Page 647
- MAY 12 South Boston Medical Society Page 647
- MAY 12 Norfolk District Medical Society Page 647
- MAY 12 Norfolk District Woman's Auxiliary Page 647
- MAY 12-14 American Association of Genito Urinary Surgeons, St. Iodge, Skytop, Pennsylvania
- MAY 13 Indications for the Use of Forceps, Dr. Roy J. Hefner, Pentucket Association of Physicians 8 30 p. m. Haverhill
- MAY 13 Massachusetts College of Pharmacy Page 647
- MAY 13 Medical Veterans of World War II Notice above
- MAY 16-22 American Board of Obstetrics and Gynecology, La. Page 344, issue of March 4
- MAY 16-23 International College of Surgeons Page 136, issue of January 22
- MAY 17-19 American Ophthalmological Society Page 492, issue of April 1
- MAY 17-20 American Urological Association Hotel Statler, Boston
- MAY 17-20 Association for the Study of Internal Secretions Page 614, issue of April 1
- MAY 17-20 American Psychiatric Association Page 614, issue of April 22
- MAY 18-22 American Association on Mental Deficiency, Copier Plaza Hotel, Boston
- MAY 20 Massachusetts Tuberculosis League, Inc. Page 647
- MAY 20-25 American Board of Ophthalmology Page 170, issue of January 29
- MAY 23-28 American Physiotherapy Association Page 543, issue of April 8
- MAY 24-26 American Gynecological Society Page 543, issue of April 8
- MAY 25-27 Massachusetts Medical Society Annual Meeting, Hotel Statler, Boston
- MAY 27-29 American Surgical Association Page 455, issue of March 11
- JUNE 2 Children's Hospital Alumni Association Notice above
- JUNE 3-6 American Orthopaedic Association Page 614, issue of April 22
- JUNE 7-10 National Gastroenterological Association Page 582, issue of March 25
- JUNE 14-16 American Neurological Association Page 455, issue of April 15
- JUNE 17-20 American College of Chest Physicians Page 455, issue of March 25
- JUNE 20 and 21 American Radium Society Page 543, issue of April 8
- JUNE 21 and 22 American Society for the Study of Sterility Page 647, issue of March 11
- JUNE 25 and 26 Christian Medical Society Page 492, issue of April 22
- JUNE 28-30 American Academy of Pediatrics, Hotel Schroeder, Milwaukee, Wisconsin
- JULY 6-24 Students' International Clinical Congress Page 455, issue of March 25
- JULY 12-17 First International Poliomyelitis Conference Page 455, issue of January 1
- AUGUST 11-21 International Congress on Mental Health Page 419, issue of March 4
- AUGUST 23-26 International Society of Hematology Page 420, issue of March 18
- AUGUST 26-28 American Association of Blood Banks Page 420, issue of March 18
- SEPTEMBER 7-11 American Congress of Physical Medicine Page 420, issue of April 15

(Notices concluded on page xiii)

The ultimate success of the repair depends upon the observance of two important steps in the technic. In the first place, the hernia sac must be eliminated. This is accomplished in the majority of cases by means of a series of plicating sutures of silk placed in the free peritoneal portion of the sac in a circumferential direction (Fig 2B and 2C). Before this layer is inserted, it is often possible to free much of the sac from its attachment to the underlying wall of the stomach near the cardia. This serves to make plication of the sac easy, but is not essential to the success of the procedure. It is not necessary to open or to remove the sac in the average case.

In a few cases, however, it will be found that the enlargement of the peritoneal reflection that forms the major portion of the wall of the hernia sac has developed far beyond the extent of the stomach into the chest. In such cases a large redundant portion of the sac can be freed and removed. The base of this type of sac must, of course, be closed either by a suture ligature or by means of a series of mattress sutures. The remainder of the sac is then plicated in the usual way.

Occasionally, when the sac is a large one, it is necessary to insert two layers of plication sutures to maintain a reduction of the hernia. If the sac

put more of these sutures to the left than to the right (Fig 2D and 2E). One layer usually suffices, but two layers may be necessary if the diaphragm is unusually thick. It is unwise, however, to apply a second layer if it produces any tendency to roll the edge of the diaphragm up onto the esophagus, because of the danger of causing an angulation just above the gastric cardia. The repair can be given greater strength and permanency by the insertion

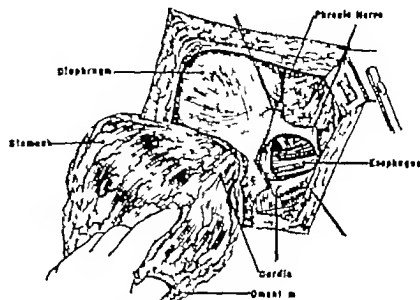


FIGURE 4. Diagram illustrating the method suggested in cases in which the enormous size of the hernia makes it difficult to maintain reduction while the repair is being carried out. The stomach and omentum have been pulled out through a counterincision in the diaphragm. After repair of the hernia has been completed the stomach and omentum will be replaced in the abdomen and the opening in the diaphragm closed.

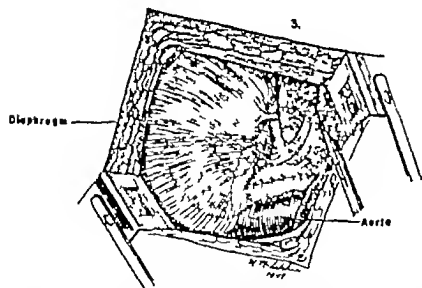


FIGURE 3. A view of the left hemithorax before closure of the chest wall incision.

Suture of the opening in the mediastinal pleura is shown after completion of the repair.

has been properly inverted by plication or removed, the hernia remains reduced with the cardia at or just below the level of the hiatus (Fig 2C).

The second important step of the operation is to narrow the hiatus to such a size that the reduction of the hernia can be held permanently. This is accomplished by means of several sutures of heavy silk placed solidly through the muscle wall behind each edge of the hiatus. Because of the natural transverse direction of the opening in the majority of cases, these sutures must be placed at each side of the esophagus. It is usually necessary, because of the relation of the esophagus to the opening, to

of a reinforcing suture of fascia lata obtained by an assistant from the patient's left thigh.

In narrowing the hiatus of the diaphragm it is necessary to exert great care to avoid a constriction that might lead to delay in the passage of food through the esophagus at that level. A good rule to follow is that if the index finger of the surgeon can easily be inserted beside the esophagus, the correct size of the opening has been established. By adherence to this rule, postoperative dysphagia has been avoided in all cases.

To complete the operation, the mediastinal pleural incision is closed with fine-silk sutures, and the edges of the pleura reattached to the diaphragm near the hiatus (Fig 3). The lung is then expanded by the anesthetist, and the chest-wall incision is closed in the usual fashion, interrupted silk sutures being used.

#### DIFFICULTIES ENCOUNTERED

In certain cases in which the hernia is unusually large, consisting of almost the entire stomach, a large part of the transverse colon, the great omentum and sometimes a portion of the small intestine as well, it is impossible to maintain a state of reduction while the repair is being made. In some of these cases, as in certain enormous scrotal hernias,

case, but in the majority it is ovoid rather than round. This fact favors the placing of the sutures used to produce a narrowing of the opening. Also, in the majority of cases the direction of this ovoid enlargement of the hiatus is transverse or oblique

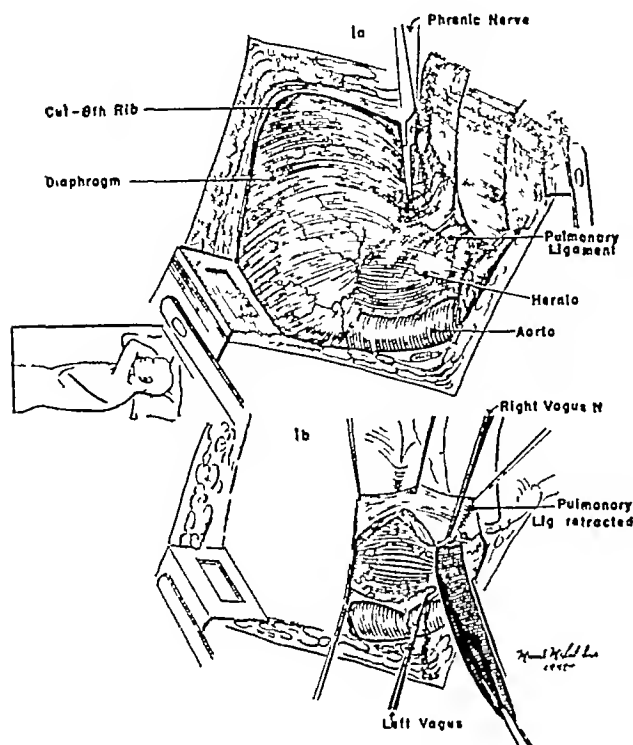


FIGURE 1 A Shows the Exposure of the Operative Field Obtained by Incision through the Left Hemithorax, Excising the Eighth Rib, and B Dissection of the Hernia, the Lower Esophagus and the Margins of the Esophageal Hiatus after Incision of the Mediastinal Pleura (Inset Direction of the Incision on the Chest Wall)

Rarely is it anteroposterior. This fact must likewise be borne in mind when sutures are being placed.

In rare cases there is a congenital absence of a portion of the diaphragm, which should normally make up a part of the margin of the hiatus. The correction of this condition presents technical difficulties that offer further opportunity to demonstrate the superiority of the thoracic approach. It is highly improbable that such a defect could be corrected through an abdominal incision.

#### DESCRIPTION OF THE OPERATION

With the patient lying on the right side and the left arm drawn up in front of his face, a long oblique incision is made across the left side of the chest in the direction of the ribs. Because of the fact that the majority of patients with hiatus hernia who require surgery are of middle age or older and therefore have an inflexible chest wall, it is better to resect a rib than to attempt to obtain sufficient exposure by an intercostal incision. Resection of the eighth rib gives the best results in the average case.

A rib spreader is inserted, and the lower lobe of the lung is retracted. The exposure obtained by this means is illustrated in Figure 1. The hernia sac and contents are easily identified lying beneath the pulmonary ligament and the pleural reflection over the lower mediastinum (Fig 1A).

The left phrenic nerve is crushed with a hemostatic forceps at the point where it leaves the surface of the pericardium to enter the diaphragm. The tranquility of the diaphragm thus induced not only assists in the performance of the operation itself but also, by ensuring temporary inactivity of the muscle, encourages firm healing of the structures that have been sutured. When the abdominal approach is used, this step must be performed through an incision in the neck, as Harrington<sup>1</sup> advocates.

The mediastinal pleura overlying the hernia is incised longitudinally and removed from its attachment around the margin of the hiatus. The hernia

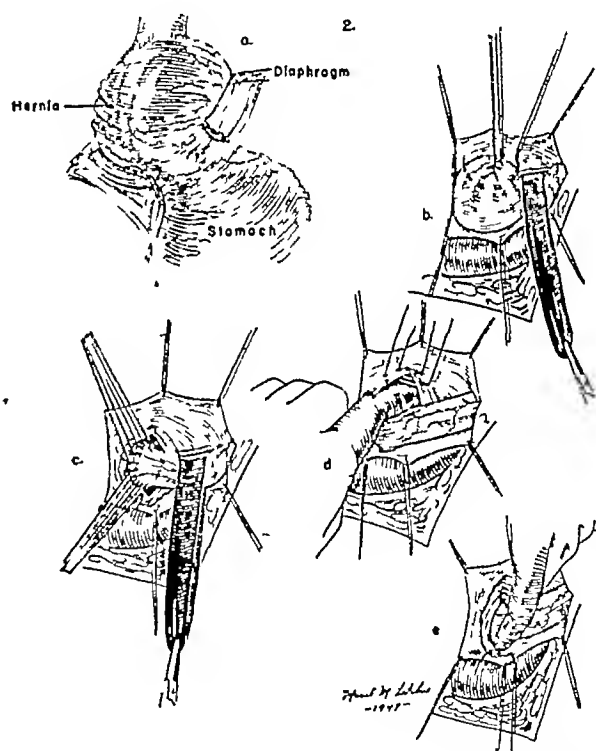


FIGURE 2 A Is a Diagram Illustrating the Most Frequent Type of Hernia, with an Apparent Shortening of the Esophagus Brought about by the Upward Thrust of the Herniated Portion of the Stomach, the Sac Consisting of a Reduplication of Peritoneum over the Anterior Aspect of the Herniated Stomach. B Demonstrates the Beginning of the Repair, Showing Plication Sutures Used to Infold the Peritoneal Sac. C Shows Complete Reduction of the Hernia Produced by Obliteration of the Sac, with Plication Sutures Already Tied but not yet Cut. D and E Illustrate Placement of the Sutures Used to Narrow the Esophageal Hiatus.

sac, the herniated portion of stomach, the lower end of the esophagus and the overlying vagus nerves are freed by dissection. The margins of the hiatus are identified and cleared of the areolar tissues that are found attached to them (Fig 1B).

The ultimate success of the repair depends upon the observance of two important steps in the technic. In the first place, the hernia sac must be eliminated. This is accomplished in the majority of cases by means of a series of plication sutures of silk placed in the free peritoneal portion of the sac in a circumferential direction (Fig 2B and 2C). Before this layer is inserted, it is often possible to free much of the sac from its attachment to the underlying wall of the stomach near the cardia. This serves to make plication of the sac easy, but is not essential to the success of the procedure. It is not necessary to open or to remove the sac in the average case.

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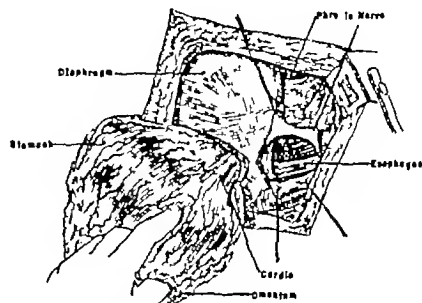


FIGURE 4. Diagram illustrating the method suggested in cases in which the enormous size of the hernia makes it difficult to maintain reduction while the repair is being carried out. The stomach and omentum have been pulled out through a counterincision in the diaphragm. After repair of the hernia has been completed the stomach and omentum will be replaced in the abdomen, and the opening in the diaphragm closed.

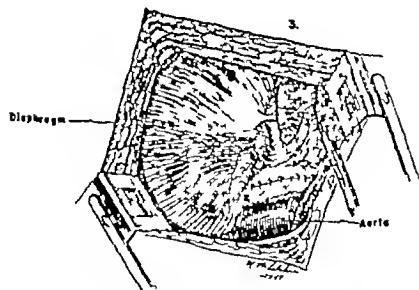


FIGURE 3. View of the Left Hemithorax before Closure of the Chest Wall Incision. Suture of the opening in the mediastinal pleura is shown after completion of the repair.

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there seems to be insufficient room within the abdomen for the long-displaced viscera. To overcome this difficulty it is necessary only to make a short counterincision in the diaphragm well away from the hiatus. Through this incision the herniated viscera are easily pulled into the abdomen and if necessary out over the lower edge of the thoracic incision, where they are protected with a pad of wet gauze (Fig 4). The sac can then be dealt with, and

TABLE 1 *Indications for Operation in 51 Patients Operated upon for Hiatus Hernia*

INDICATION	NO OF CASES	PER-CENTAGE
Intractable pain	35	68.6
Blood loss	7	13.7
Chronic	5	9.8
Acute	2	3.9
Incarceration with or without obstruction	9	17.6

the opening in the hiatus reduced to proper size with less difficulty than in the average case. After the repair of the hernia has been completed, the viscera are replaced in the abdomen and the incision in the diaphragm is closed. If the sutures used to close this incision tend to pull through the tissues because of the increased pressure within the abdomen, a strip of fascia lata will overcome the difficulty.

It sometimes happens, when sutures are placed across the hiatus to the right of the esophagus, that the branch of the right vagus nerve that passes to the celiac ganglion interferes. In such a case, this

TABLE 2 *Complications Following Supradiaphragmatic Repair of Hiatus Hernia of the Diaphragm (51 Patients)*

COMPLICATION	NO OF CASES
Empyema	1
Thrombophlebitis of leg veins	3
Sublethal pulmonary embolism	1
Minor wound sepsis	1
Total	6*

\*Five patients.

branch of the nerve should be divided. No untoward result has been observed to follow this maneuver in the few cases in which it has been necessary.

If the esophagus is actually too short and a portion of the stomach is therefore congenitally thoracically placed, no attempt to change the situation should be made. Furthermore, it is not necessary in such cases to elevate the diaphragm in an attempt to relieve the patient. The pain is eliminated if the peritoneal sac is removed, after it has been dissected free from the stomach, or if it is thoroughly inverted below the level of the hiatus.

## POSTOPERATIVE CARE

The management of the early convalescence of the patient offers no special problems other than those likely to be encountered whenever a thoracotomy is performed. It is wise to leave a Levin tube in the stomach during the first forty-eight hours to prevent gastric dilatation. The patient should be fed with caution at first, but a normal diet is usually tolerated by the seventh or eighth day. Early ambulation is encouraged. The majority of patients are out of bed from the second day on. The average period of hospital stay after the operation is twelve and a quarter days.

## CLINICAL EXPERIENCE

The operation described above has been used in the treatment of 51 patients with hiatus hernia of the diaphragm. In every case an important indication for the operation existed. In the majority of cases the reason for operation was the occurrence of severe attacks of pain, which could not be con-

TABLE 3 *Late Results of Supradiaphragmatic Repair in 43 Patients Operated upon Six Months or More Ago*

RESULT	NO OF CASES
Incisional discomfort	
Severe	0
Slight	4
None	36
Not stated	3

trolled by dietary or medicinal means. In a few cases a severe degree of blood loss, usually of a chronic nature, provided the indication for surgery. In the remainder there was incarceration of the hernia, usually with obstruction, either intermittent or complete (Table 1).

Postoperative complications occurred in 5 patients (Table 2). One patient, whose operation was performed early in the series before penicillin was available, developed a localized empyema, which required drainage. Thrombophlebitis of the leg veins developed in 3 cases, in 1 of which a sublethal pulmonary embolism occurred. The only other complication consisted of minor, superficial wound infection, which was not serious enough to delay discharge from the hospital.

In a comparable series of 25 cases of hiatus hernia repaired at the Massachusetts General Hospital by other surgeons using the abdominal approach, there were complications in 7 cases and 1 postoperative fatality.

There were no postoperative deaths among the 51 patients operated upon transthoracically.

For the information of those who may hesitate to use the thoracic approach because of the fear that the incision may remain painful for a long period after the operation, a careful inquiry was made of

all the 43 patients whose operations were performed six months or more ago. A definite statement was obtained from 42 of these patients. In no case had there been any severe pain after the immediate postoperative period. Four of the patients reported slight discomfort, but 38 patients experienced no discomfort from the incision after the first few weeks (Table 3).

### RESULTS

Eight patients have been operated upon so recently that a follow-up study of the result would hardly be significant. The remaining 43 patients, however, were operated upon six months or more ago, and the results of a recent study of their present status are illustrated in Table 4. Criteria for evaluation of the end result in these cases have been based upon the statements of the patient and his physician regarding the relief of symptoms and, whenever possible, upon roentgenographic evidence obtained by the ingestion of barium. In none of these cases has a definite recurrence of the hernia been demonstrated by roentgen-ray studies. In 1 patient there is evidence still of a slight protrusion of the cardiac end of the stomach above the hiatus. In this case, however, the reduction of the herniated stomach was incomplete at operation because of an abnormally short esophagus. Furthermore, the patient, who was a chronic invalid because of the severity of the pain before operation, is now cured of the pain caused by the hernia. He continues to have occasional attacks of angina pectoris from known pre-existing coronary-artery disease. In another patient there is an equivocal shadow in a roentgen ray film obtained several months after operation. This case is classified as suggestive of recurrence although the symptoms were completely relieved by the operation.

The failure to relieve the discomfort in 1 case may mean that the symptoms were erroneously ascribed to the hernia. At any rate, no roentgen-ray evidence of recurrence has been observed in this patient. The same thing may be said for the 3 patients who are only partially relieved of discomfort. In all the other 39 patients, including those who had bled and those with an incarceration of the hernia, as well as those who had pain only, the relief of symptoms has been complete and permanent (Table 4).

Soutter<sup>2</sup> found after a review of 24 cases of hiatus hernia repaired through the abdomen at the Massachusetts General Hospital that a large number had apparently recurred, often before the patient left the hospital. In the 9 patients of this group who had subsequent investigation by roentgen-ray studies a definite recurrence was observed. On the other hand, of the 43 patients operated upon by the thoracic approach six months or more ago, 95.5

TABLE 4 Late Results of Supradiaphragmatic Repair in 43 Patients Operated upon Six Months or More Ago

RESULT	No. of Cases
Evidence of recurrence:	
Definite	0
Suggestive	1
Hernia not reduced completely at operation	1
None	41
Symptomatic relief:	
Complete	39
Partial	3
None	1

per cent show no suggestion or evidence of recurrence. This result, when compared with the results obtained by the use of the abdominal approach, at least among the cases observed at the Massachusetts General Hospital, demonstrates the superiority of the supradiaphragmatic operation.

### CONCLUSIONS

The widely prevalent belief among physicians and some surgeons that an operation for the repair of hiatus hernia of the diaphragm, especially when performed by the thoracic approach, is unusually dangerous or attended by a high incidence of complications is erroneous.

The widespread impression among physicians and surgeons that the repair of a hiatus hernia of the diaphragm is likely to be followed by a high incidence of recurrence is based upon experience with the abdominal approach and does not apply when the supradiaphragmatic operation is used.

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1. Harrington S. W. Surgical treatment of more common types of diaphragmatic hernia: esophageal hiatus, traumatic, pleuro-peritoneal hiatus, congenital abscess and foramen of Morgagni: report of 404 cases. *Ann. Surg.* 122:546-568, 1945.
2. Soutter L. Analysis of cases of hiatus hernia treated by surgery at Massachusetts General Hospital. *5. Clin. North America* 27:1121-1127, 1947.

# PROLONGED PAROXYSMAL AURICULAR TACHYCARDIA

## Report of a Case Including Treatment with Veratrum Viride

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BOSTON

THERE have been several reports in the literature of cases of prolonged paroxysmal auricular tachycardia. The case reported below is presented because it is somewhat rare and it is the first case in which veratrum viride has successfully though temporarily stopped an episode of tachycardia.

Peterman<sup>1</sup> reported a quite similar case in a six-year-old child who developed an auricular rate of 160 in November, 1943, and at the time of the study (January, 1946) the tachycardia had persisted. Digitalis was given until toxic effects were produced without stopping the tachycardia, mecholyl produced only temporary conversion to normal rhythm, and papaverine, ipecac, quinidine and intravenous magnesium sulfate were without effect. An inflated blood-pressure cuff about the neck caused an immediate conversion to normal sinus rhythm, but the paroxysmal auricular tachycardia returned the next day. There was no known cause of the tachycardia, though it was first noted after several very severe upper respiratory infections.

Mayer<sup>2</sup> described a case in a ten-year-old girl who had had a persistent tachycardia starting at the age of one. There was no known precipitating cause.

Piotti<sup>3</sup> reported a case in a child first observed at the age of eleven months in an episode lasting twenty-three days. A later attack lasted seven months. Various therapeutic agents were tried, including digitalis, quinidine and ergotamine tartrate, none of which had any effect. The patient finally died in congestive heart failure at the age of eighteen months. Histologic examination of the heart at autopsy revealed an interstitial myocarditis of the Fiedler type. The lesion was located only in the right auricle and in the region where the fibers of connection run from the ostium of the coronary sinus to the node of Aschoff-Tawara.

Mahaim<sup>4</sup> reported a case very similar to that of Piotti, in a fourteen-month-old child who developed the condition after a respiratory infection. The initial paroxysm lasted fifteen days and was followed by another during which the child died of bronchopneumonia. Post-mortem examination revealed some recent inflammatory lesions of the Keith-Flack node.

Cooke and White<sup>5</sup> reported an episode in an infant aged eighteen months that lasted over twelve months without any apparent ill effects. This was the only case of long duration in their series of 600 cases.

Olney<sup>6</sup> has seen several cases of prolonged paroxysmal auricular tachycardia in children, usually after infectious diseases. She states that the cases are usually benign and terminate spontaneously and are better left untreated if the heart is otherwise normal.

In adults, Hamilton and Hurwitz,<sup>7</sup> Herson and Willington,<sup>8</sup> Maddox<sup>9</sup> and Miller and Perelman<sup>10</sup> have reported cases. In reviews of large series of cases Gallavardin<sup>11</sup> found that 11 out of 160 patients had attacks lasting as long as ten days, 4 of these cases lasted over a month. None of the patients died during the attacks. Campbell<sup>12</sup> found 2 cases in his series of 100 that lasted longer than ten days. Hume<sup>13</sup> reported that only 1 of a series of 48 cases lasted over ten days. Levine<sup>14</sup> has followed a patient who had paroxysmal auricular tachycardia for twenty years, the auricular rate persisted at 240, and the ventricular rate was usually 120 but occasionally 60 or 240. Bouveret,<sup>15</sup> in the classic early article on paroxysmal auricular tachycardia, described a case lasting thirteen days.

## CASE REPORT

J. C., a 3-year-old boy, was first seen in the South Department of the Boston City Hospital for an acute pharyngitis and otitis. He received symptomatic treatment with prompt recovery. The heart rate and rhythm were normal at that time. He was next seen at the age of 5 on February 4, 1947, with a history of nasal discharge for 2 days and sore throat for 1 day.

There was no past history of any joint pains or palpitation. The family history was noncontributory, with no history of heart disease. The mother was 24 and the father 27 years of age, both were living and well. Four younger siblings were also living and well.

Physical examination disclosed a well developed and well nourished boy. There was a tonsillar membrane. The remainder of the examination was negative. The heart was not enlarged, the sounds were of good quality without murmurs, and the rate was 90 with normal rhythm.

The patient was given 30,000 units of diphtheria antitoxin intramuscularly. The nose and throat cultures proved positive for diphtheria bacilli. The membrane rapidly disappeared, and convalescence was uneventful. The patient received penicillin parenterally from March 11 to March 20 because of continued positive diphtheria cultures from the throat.

On March 18 the patient developed varicella. On April 3 the tachycardia was first noted. An electrocardiogram revealed a regular rate of 140 with inverted P waves in the limb leads. The pulse was regular, but the rate increased with emotion or exertion, it was unaltered by carotid sinus or eyeball pressure.

On April 11 the patient developed a moderate case of measles, without complications. Two days later an electrocardiogram revealed a rate of 94 with normal upright P waves except in Lead 4<sub>r</sub>, in which, after a deep breath, the rhythm changed from a paroxysmal tachycardia with upright P waves to a sinus rhythm with inverted P waves. Earlier that day and after the electrocardiogram the pulse had been 130 and regular.

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On April 21 quinidine sulfate was given. Some irregularity of the pulse was noted after the third dose of 0.2 gm. An electrocardiogram revealed occasional runs of sinus rhythm interspersed in the paroxysmal auricular tachycardia. On the following day quinidine was given up to 1.2 gm without effect.

On April 23 digitoxin was started orally. Toxic symptoms were reached, and runs of normal sinus rhythm occurred but there was no prolonged conversion. About 3.5 mg was given in 4 days. On May 1 the patient was discharged and allowed full activity at home.

On May 12 0.2 gm of quinidine was given three times daily in addition to 1 teaspoonful of potassium acetate in 25 per cent solution three times daily. Because of vomiting of the potassium acetate potassium chloride solution was tried for 4 days but without effect.

From May 23 to June 20 the patient was given 0.1 mg of digitoxin daily and 0.2 gm of quinidine three times daily only to become toxic again without converting to sinus rhythm.

On June 24 the patient re-entered the hospital for esophageal electrocardiograms and a trial of mechoyl. Large doses of phenobarbital (up to 0.15 gm three times daily) over a week were first given in an attempt to obtain sedation. This therapy effected no appreciable degree of sedation nor did it alter the tachycardia. Sodium pentothal anesthesia, 1.2 gm by rectum was given on June 26 with prompt and effective anesthesia which enabled performance of esophageal lead electrocardiograms. On July 3 mechoyl was given for the first time, the technique described by Starr<sup>14</sup> being used. With the patient lying horizontal, alternate pressure over the carotid sinuses was tried when this was fruitless mechoyl was administered. The first dosage was 1.25 mg. When the tachycardia persisted after 3½ hour a larger dose (2.5 mg) was given. A third dose of 5 mg produced facial flush and sweating about 3 minutes after subcutaneous injection. The rhythm changed to a sinus tachycardia rate of 160 with

every 1½ hour. At 7.25 p.m. the pulse rate started to fall, from the preceding 136 to 114. By 8 p.m. the rate had reached 80 and the electrocardiogram revealed normal sinus rhythm with upright P waves (Fig. 2). The pulse rate remained below 100 until 10 o'clock the next morning when it started to rise. By 3.30 p.m. the pulse was 140 with the usual inverted P waves in the electrocardiogram. There was no effect on the blood pressure, which always remained around 110/70, nor were there any subjective symptoms. On July 23 at 4.30 p.m. the patient was given one tablet of veratris. Five hours later the pulse had fallen to 92, and the electrocardiogram showed upright P waves. At 7 o'clock the next morning the pulse rate had reverted to 140. The next

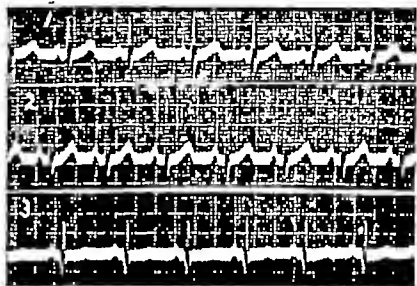


FIGURE 2. Electrocardiogram after the Administration of Veratris Showing Normal Sinus Rhythm in All Three Limb Leads

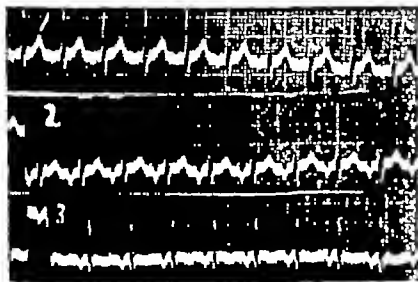


FIGURE 1. Electrocardiogram before the Administration of Veratris, Showing Paroxysmal Auricular Tachycardia in All Three Limb Leads

upright P waves in Leads 1, 2 and 3 then to a shifting pace maker for a minute and then back to the paroxysmal auricular tachycardia. On July 7 the patient was given 6.25 mg of mechoyl subcutaneously about 2 minutes later the rhythm switched from the tachycardia to a sinus rhythm at a rate of 80. He sweated, flushed, passed flatus, became nauseated and complained of abdominal pain. 0.0006 gm of atropine was given subcutaneously with prompt cessation of the side effects. The normal rhythm lasted about 10 minutes and then the tachycardia recurred.

The patient was next given a trial of veratrum viride. The first tablet of veratris\* (10 Crow units) was given on July 22 at 4.35 p.m. when an electrocardiogram disclosed paroxysmal auricular tachycardia in all three limb leads (Fig. 1). The pulse was checked every 10 minutes and the blood pressure

tablet of veratris on July 24 produced normal sinus rhythm for only 3½ hours. Another tablet of veratris that afternoon caused only a transient conversion to sinus rhythm with frequent changes from sinus rhythm to paroxysmal auricular tachycardia throughout the night. On July 25, 26, 27, 30 and 31 veratris was given — at first one tablet in the morning and one in the afternoon and then one tablet followed within 1 hour by another, there was no conversion to sinus rhythm.

On August 4 and 5 0.003 and 0.006 gm of pilocarpine were given without effect. On August 6 phystigmine (0.0006 gm) produced no effect later 0.0012 gm was given without effect. On the next day a blood pressure cuff was inflated about the patient's neck for about 20 seconds without response. On August 9 magnesium sulfate — 20 cc. in a 10 per cent solution — was given intravenously without producing a change. On August 11 one tablet of veratris was given at 9 a.m. and a second at 1.15 p.m., without effect.

Mechoyl in doses from 5 to 7.5 mg was given on August 18 and again on August 22 with a change in the rhythm to sinus tachycardia but no change to normal sinus rhythm. Each time the sinus tachycardia was soon replaced by the paroxysmal auricular tachycardia.

A tablet of veratris was tried again on October 5 without effect.

All the routine laboratory studies including blood studies (red-cell count, white-cell count, sedimentation rate and cholesterol), urinalyses and basal metabolic rate as well as x-ray films of the chest were normal.

The patient is now attending school without difficulty. The pulse continues to be rapid and regular.

#### DISCUSSION

The etiology of similar cases has been quite varied. Diphtheritic myocarditis usually occurs from the sixth to the twenty-first day after the onset of diphtheria.<sup>17</sup> It was the opinion that the case reported above probably did not represent a diph-

\*Kindly furnished by Inala, Neilsen and Company, Decatur, Illinois.



theritic myocarditis because of the late time relation and the lack of other signs or symptoms of myocarditis. In a series of 100 cases of severe diphtheria Begg<sup>18</sup> took routine electrocardiograms and found 1 case of paroxysmal auricular tachycardia. That case was fatal before the nineteenth day of the illness. Anderson<sup>19</sup> reported the case of a thirty-nine-year-old man who developed paroxysmal auricular tachycardia six weeks after a severe case of diphtheria and died within seventy-two hours of the onset of the tachycardia. In this case, however, it is probable that the patient had myocarditis much earlier.

Similar cases have been uniformly resistant to therapy. No reports in the literature state that veratrum viride has been used successfully in such a case. In a clinicopathological conference reported from the Massachusetts General Hospital<sup>20</sup> the unsuccessful use of the tincture of veratrum viride is mentioned. Collins<sup>21</sup> also reported the unsuccessful trial of veratrum viride tincture in a case of paroxysmal auricular tachycardia. The drug is not without danger and should only be used with a full knowledge of its toxic effects. The progressively diminishing response to veratrum, which probably represents tachyphylaxis, has been observed in dogs by Krayer and Acheson.<sup>22</sup>

Veratrum viride is obtained from the rhizome and roots of the plant *Veratrum viride*, commonly known as the green hellebore. It contains a mixture of alkaloids, the most important of which is protoveratrine. The main actions of veratrum are slowing of the heart rate, a fall in systemic blood pressure, slowing of the respiratory rate and a "collapse reaction" characterized by sweating and reduction in body temperature. Poisoning by the drug is characterized by nausea and vomiting, diarrhea, headache and cardiovascular collapse. Large doses of veratrum are rapidly vomited, however, so that death is rare. The site of action of the drug is believed to be the vagal nuclei in the medulla and the afferent nerve endings of the vagus nerve. Atropine will abolish the effects of veratrum and should be at hand in the event of an overdose.

### SUMMARY

A case of prolonged paroxysmal auricular tachycardia in a five-year-old boy two months after a moderate attack of diphtheria and two weeks after

an attack of varicella is presented. The paroxysmal tachycardia has persisted to date except for occasional, transient spontaneous conversion to normal sinus rhythm and has been temporarily converted to sinus rhythm by mecholyl and veratrum viride.

Digitalis, quinidine, potassium acetate, potassium chloride, physostigmine, pilocarpine, magnesium sulfate, carotid-sinus pressure, eyeball pressure, sedatives and a blood-pressure cuff inflated about the neck were without effect on the tachycardia. The patient has been asymptomatic throughout the duration of the tachycardia and is leading an active life. At no time has he shown any signs of cardiac enlargement or decompensation.

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## FOOD SENSITIVITY IN 100 ASTHMATIC CHILDREN\*

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THAT food can cause asthma in children is a fact beyond dispute. The frequency of this sensitivity, as well as its relative importance to recurrent respiratory infection, sensitization to pollens and other environmental allergens, is an entirely different question, concerning which there is considerable difference of opinion.

An example of the way allergy is not infrequently treated is provided by the history of an asthmatic child of five years who was recently seen. She had previously been treated in another city and brought with her a typed list, bound in the form of a small book, of the foods that she could and could not eat, as determined by skin tests. The "good" foods were typed in black, and the "bad" foods in red, it was all very impressive. She had been tested with two hundred and thirty-six foods, including squab, tripe, calves' brain, venison, caviar, poppy seed, elderberry, pheasant, bops, chives and Limburger cheese, and had been found allergic to one hundred and nine of them, including Sanka coffee, rutabaga, German celery, thyme, cranberry, sand dab, tripe, sweetbreads and watercress. Among the foods she was allowed to eat were pheasant, guinea hen, venison, horse meat, turtle, abalone, terrapin, caraway seed, juniper, avocado, mango and quince. The asthma was in reality due to grass and tree pollen, and she was later quite successfully hypo-sensitized, with no dietary restrictions whatever.

This is by no means an isolated example. Too many people, without proper training or common sense, treat allergy in this way. Food allergy in particular lends itself to exploitation, for a dietary "cure" of any sort is a form of therapy that has made a great impression on the laity from time immemorial, and some of the greatest fads and mis-conceptions in medicine have had "diets" as their basis.

That sensitization to food is a common cause of allergic symptoms is certainly true, that too much pseudo-science and too little common sense are too often used in dealing with foods as allergens is equally true.

The general interest in diets as such, the tendency to attribute to the ingestion of foods all manner of complaints, the deep impression made by the occasional instance in the asthmatic of the sudden sharp often danger-ously severe attack following the eating of a specific food combine to give undue consequence to food allergy as a cause of asthma.<sup>1</sup>

To determine the influence of food upon asthma is by no means easy because there are so many

extraneous complicating factors involved, and no statistics can be really accurate.

For the purposes of this study, 100 asthmatic children between the ages of three and twelve years, partly from the clinic and partly from private practice, were observed and were tested by the scratch method. Thirty-five gave one or more positive tests to foods, and 65 gave none. There was no reason to believe that asthma was caused by food in any of those who gave negative tests; the asthma could be accounted for in other ways (such as animal emanations, pollens and upper respiratory infections). It is recognized, however, that asthma may be rarely caused by a food and that there may still be a negative skin test; the bronchial mucous membrane is sensitized, and the skin is not. In children this situation is believed to be rare, it is hardly ever necessary to employ elimination diets in the presence of negative skin tests to determine food sensitivity in the study of an asthmatic child. It is also recognized that an intracutaneous test to a food is often positive when the scratch test is negative. It was formerly the custom in this clinic to do routine intracutaneous tests with foods in all the asthmatic children. There were so many positive reactions that meant nothing clinically and it was so rare to obtain any information of value that this procedure was given up. Intracutaneous tests with environmental allergens, particularly with pollens, when scratch tests are negative, are, however, of great value, and when positive usually indicate clinical sensitivity.

Very few of the children in this series had continuous asthma—in almost all there were periods of at least three or four weeks when they were free from it. If they were eating the foods in question daily or frequently during these periods and no asthma was produced, it was concluded that the foods were harmless so far as asthma was concerned. If the child was having nearly continuous asthma, the reacting foods were removed from the diet and reintroduced one at a time during asthma-free periods, and the results noted. If there was any suspicion of a food that was eaten infrequently, this was given in ordinary amounts, and if no asthma occurred within forty-eight hours, it was concluded that the food in question had nothing to do with the asthma. There were a few cases of very large skin reactions to fish or nuts in which this test was not done, since I did not wish to run the risk of producing a dangerous reaction with these potent allergens. The food question was discussed frequently and for considerable periods with the mothers, for most of the children were being brought

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in for inoculations each week. It was almost always found that the mother knew from previous experience what foods produced asthma.

In 24 of the 100 children studied asthmatic attacks had been or could be produced by the ingestion of a specific food. In most cases this had been recognized by the mother before the child was seen, and the food or foods in question had been removed from the diet, so that there were not many cases in which food was concerned in producing the asthma at the time the child was brought in.

In the 100 children there were 218 positive scratch tests to foods (Table 1). Of these, there were 44

in 2. No symptoms were caused by one hundred and fifty-eight foods (72 per cent) to which tests showed skin sensitivity. It is probably true that asthma would have been produced in some of these patients had a considerable amount of the food been ingested. Not uncommonly, however, the degree of sensitivity to some of these foods, such as fish and nuts, is so high that as soon as any of the food touches the lips or enters the mouth, the mucous membrane begins to swell, and the food is immediately spat out or regurgitated before there has been any chance for it to be absorbed. If these cases are included, the number of foods producing asthma is increased from forty-four to sixty.

### DISCUSSION

These figures agree with those of Adams<sup>2</sup> and of Chobot and Hurwitz.<sup>3</sup> Adams found that of 130 positive scratch tests to foods in a group of allergic children, 23 per cent were of clinical significance. Chobot and Hurwitz observed that 18 per cent of 198 positive scratch tests to foods in 38 allergic children were of clinical significance.

It seems well established, therefore, that only about a fifth of the positive scratch tests to foods in asthmatic children have anything to do with the asthma, and furthermore that, although it is possible for clinical sensitivity to any food to exist in these children and to be at least a contributing factor to the asthma, the number of foods that cause such sensitivity with any frequency is not large (fish, egg, nut, peanut and chocolate), as a rule, a high degree of sensitivity must exist for a food to cause asthmatic attacks. Wheat and milk, which may be of considerable importance in the atopic dermatitis of infants and in many other allergic conditions, rarely caused asthma in the children under consideration, and positive scratch tests were not common (Table 1).

In asthma, positive skin tests to environmental allergens are usually of etiologic significance; the mucous membrane of the respiratory tract, as well as the skin, becomes easily sensitized to these allergens. To cause a positive skin test to a food, unsplit food protein must at some time have entered the blood stream, and in atopic people an immunologic reaction results, which is manifested by a positive skin test. The respiratory mucous membrane is likely to escape sensitization, the immunologic reaction is shown only on the skin, and possibly by the presence of reagins in the blood serum. Positive tests to foods have the same significance as positive tuberculin, trichophyton or brucella tests: at some time the organism has been exposed to antigenic material, and an immunologic reaction, which may or may not have anything to do with the clinical condition under consideration, has occurred. One would expect, however, that if there were a high degree of skin sensitivity, as in many of the nonetiologic tests, if the food were eaten,

TABLE 1 *Results of Skin Tests to Foods in 100 Asthmatic Children*

Food	TOTAL NO OF POSITIVE TESTS	ASTHMA	VOMITING AND HIVES*	NO SYMPTOMS
		NO OF CASES	NO OF CASES	NO OF CASES
Apple	3			3
Asparagus	4		1	3
Banana	5		1	4
Barley	5	1		4
Beef	4			4
Carrot	0			
Celery	6			6
Chicken	8			8
Chocolate	5	4		1
Corn	5	1		4
Egg white	21	6	5	10
Fish	25	12	2	11
Lamb	3			3
Milk	1			1
Oat	4			4
Orange	5	1	2	2
Peanut	12	10	1	1
Pea	6			6
Pork	2			2
Potato	22			22
Rice	3			3
Rye	8			8
Spinach	27	1	1	25
String bean	6			6
Tomato	9	2		7
Wheat	5			5
Walnut	15	6	3	4

\*No asthma caused by foods in these cases.

(20 per cent) in which it was definitely proved that the food in question could cause asthma. It is especially noteworthy that egg white, fish, peanut, walnut and chocolate accounted for 38 of the 44 etiologic tests. The other foods producing asthma were tomato in 2 cases, spinach in 1, orange in 1, corn in 1 and barley in 1. Although potato gave 22 positive tests (some of them large wheals with pseudopods), in no case could it be shown that the ingestion of potato produced asthma or any other symptom. Since the first days of skin testing, spinach extracts have always been nonspecifically irritating, and it is probable that a large proportion of the positive tests to spinach were of this character. It did cause asthma in 1 patient, however. In 16 cases (8 per cent) a food that gave a positive test caused irritation about the mouth, vomiting, urticaria or angioneurotic edema, but no asthma. This was true of asparagus and banana in 1 case each, egg white in 4, fish in 2, orange and peanut in 1 each, spinach in 2 and walnut

dermatitis or urticaria would result, inasmuch as the skin is sensitized. Nevertheless, in 218 cases of positive tests in the series of children under discussion, the corresponding food could be eaten with complete impunity in 158—there was no asthma, urticaria or eczema, in spite of the fact that in many of these patients the skin showed a high degree of sensitization.

Some of the positive tests had been of etiologic significance when the child was younger, and with increasing age he had become "tolerant" to the food, some of them had never been of etiologic significance. There is a great tendency in allergic children to acquire tolerance to foods as they grow older. Many children who have violent symptoms from egg white at the age of a year, can eat it with impunity at the age of six years, but the positive skin test often persists, and the reaction may be as large as it was in the beginning. Tolerance to environmental allergens does not come so readily; the child clinically sensitive to cat hair or to ragweed pollen is likely to remain sensitive for a long time, often through life.

The immunologic situation in these children who are tolerant to foods in the presence of large positive skin reactions, and who often have reagins of high titer as well, is not clearly understood, nor is the mechanism by which they acquire this tolerance. If absorbed food protein reaches the skin, urticaria or dermatitis should result. Therefore, either unsplit food protein is not absorbed in sufficient quantity to cause a reaction, or some mechanism has been developed by which it is rendered innocuous after it has been absorbed. It must be remembered, however, that a very high degree of skin sensitivity must be present before urticaria can result from an ingested food, and that the solutions used by outside application or intracutaneous introduction in testing, which produce whealing reactions, are probably many times more concentrated than the concentration of a small amount of absorbed food protein when it has been diluted in the several liters of blood contained in the body. If the degree of skin sensitivity is very high, however, an infinitesimal amount of absorbed allergen may cause whealing. Brunner and Baron<sup>4</sup> found, for example, that the intravenous administration of cottonseed extract containing 0.0001 mg of nitrogen caused an urticarial reaction on skin sites that had been artificially sensitized with a serum containing a high titer of cottonseed reagin. When diluted with the amount of blood plasma contained in an adult (approximately 3000 cc.), this would mean a dilution of 1:30,000,000. Walzer<sup>5</sup> found that 0.0001 mg of nitrogen represented 1/5600 of one cottonseed. So that with a very high degree of skin sensitization it is necessary for only traces of food protein to be absorbed to cause urticaria.

It is a fact that any food protein can be absorbed unsplit—if this were not so there would be no

positive skin tests to foods. It is also a fact that this absorption can happen at any age and probably true that there is a considerable difference in the ease with which various food proteins are absorbed—for example, fish, nut and egg protein are consistently absorbed by many people. Not much is known about other foods, however, and it is not unlikely that with many people the unsplit protein of many foods is absorbed only for a short time when the food is first eaten, enough for the development of an immunologic reaction, evidenced by a positive skin test—no more after that, or at any rate not enough to cause a reaction except possibly if an excessive amount of the food is eaten. Some people, however, seem to absorb the unsplit protein of a number of foods over long periods; if this were not so there would be no asthma from food, no dermatitis, no urticaria and no migraine. It seems likely that there is a great individual variability in this respect.

If unsplit food protein reaches the skin in sufficient amount and the skin is strongly sensitized, some skin manifestation should result. Therefore if no reaction takes place, the protein has not been absorbed in sufficient amount, or at all, or it has been changed after absorption in some way so that it is no longer antigenic.

In asthma the situation is somewhat different, for the bronchial mucous membrane may not be sensitized. If it is sensitized, the situation in asthma may be compared to that in dermatitis: either failure of sufficient absorption or neutralization after absorption.

## CONCLUSIONS

About a fifth of positive scratch tests to foods in asthmatic children are of etiologic significance.

The mother usually knows what food produces asthma, and has omitted it before skin tests are done.

Theoretically, any food can cause asthma, practically, not many foods commonly do so. Fish, egg, walnuts, peanuts and chocolate are the most important. Wheat and milk can cause asthma in children, but do not often do so.

Sensitivity to food, which should always be taken into consideration in asthmatic children, is of relatively little importance in comparison with sensitivity to pollen, other environmental allergens and upper respiratory infections.

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## GENERALIZED EXFOLIATIVE DERMATITIS DUE TO PENICILLIN\*

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THE increasing frequency of reactions to penicillin warrants wider recognition of the dangers of the local application of penicillin, and more reliance placed on less sensitizing methods of administration, such as the intramuscular, intravenous and intra-arterial routes<sup>1,2</sup>. Although the direct toxic action of penicillin is negligible,<sup>3</sup> aside from the irritating effect when the drug is applied to the central nervous system,<sup>4</sup> the delayed or acquired sensitivity reactions may be severe or fatal. Wile<sup>5</sup> noted that severe allergic reactions involving edema of the pharynx, larynx and lungs complicating penicillin therapy are serious and may result in fatal complications. Numerous other authors have reported severe reactions simulating asthma,<sup>6</sup> serum sickness<sup>7,8</sup> and epidermal reactions such as bullous dermatitis.<sup>9</sup> Kolodny and Denhoff<sup>10</sup> have stated that patients with dermatologic disorders have a higher sensitivity than other patients. Gottschalk and Weiss<sup>11</sup> noted that a delayed or acquired sensitivity could be produced by repeated local applications of penicillin. By using a simple patch test they were able to sensitize 4.5 per cent of 200 persons to penicillin ointment. Pillsbury<sup>12</sup> states that the incidence of sensitivity reactions at present is over 15 per cent, and he believes that this percentage may increase as the incidence of exposure to penicillin is increased. The fact that these reactions are not limited to local manifestations but that severe generalized eruptions occur often escapes due consideration. Cormia<sup>13</sup> noted severe systemic involvement in patients after the local application of penicillin, and Barksdale<sup>14</sup> reported a fatal case of exfoliative dermatitis due to penicillin therapy. Barksdale's patient did not have syphilis and had become sensitized to penicillin therapy while at sea. He was also sensitive to sulfonamides. He was given 100 units of penicillin every three hours, for a cellulitis of the skin, but at the end of the seventh dose the administration of penicillin had to be discontinued because of a severe cutaneous eruption, which progressed into a generalized exfoliative dermatitis, streptococcal septicemia and death. Because of this and other toxic reactions complicating the use of penicillin locally for the treatment of skin diseases, Barksdale concludes that "penicillin locally in any form is absolutely contraindicated." The following case is reported as further evidence that complications dangerous to life may result from the local use of penicillin.

## CASE REPORT

A 27-year-old man with no history of allergic disorders or previous penicillin therapy, was seen in the outpatient clinic of an Army hospital ship on November 14, 1946.

\*The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Army Medical Department.

Physical examination disclosed typical impetigo contagiosa of the skin, with honey-like crusted lesions on an erythematous base on the left side of the neck.

The patient was instructed to wipe the area twice daily with alcohol and after this had dried to apply penicillin ointment in a petrolatum base (1000 units per cubic centimeter) locally. The lesions retrogressed and the patient improved during the first 3 days of therapy, but on the 4th day coalescing vesicular lesions covered with a honey-like material on an erythematous base spread further on the left cervical region and appeared at the right angle of the mouth. He was admitted to the hospital, and local therapy was continued with penicillin ointment. Two days later the individual lesions had improved, but an erythematous lesion had appeared involving the skin more deeply and covering the entire area over which the ointment had been applied. This sharply demarcated area was erythematous, edematous and indurated, and there was an increase in local temperature. There was no systemic toxicity, however, to suggest a true erysipelas. Local penicillin therapy was discontinued, and Burrows boric acid wet soaks were given as the only treatment. On the following day the erythematous lesions had spread further on the neck so that 30,000 units of penicillin every 3 hours was started intramuscularly in addition to the local wet compresses. No improvement of the local lesions resulted, and on November 22 severe pruritus of the involved area occurred. On November 23 a fine maculopapular generalized eruption was noted with a more erythematous reaction over the scrotum and inner aspects of the thighs. A diagnosis of dermatitis medicamentosa was made, and the intramuscular administration of penicillin was discontinued immediately. Phenolated zinc lotion was used to control the intense associated pruritus. The skin lesions deepened in color, and within the next 7 days a generalized exfoliative reaction of the entire body, including the palms, soles, scalp and eyelids, occurred.

The patient subsequently had no difficulty, but he was cautioned against receiving penicillin in any form again. An interesting therapeutic note was that the impetigo of the face and neck never disappeared on either local or intramuscular administration of penicillin, but disappeared after 5 days of therapy with ammoniated mercury ointment.

## DISCUSSION

This case demonstrates that systemic sensitization to local applications of penicillin may rapidly occur so that severe generalized reactions are not prevented by a change to parenterally administered penicillin. The potential dangers of penicillin applied locally more than offset any advantages of this mode of therapy. Generalized exfoliative dermatitis is a complication to be feared and should not be risked by the local application of penicillin ointment to an innocuous skin lesion. In the case reported above continuation of intramuscular penicillin after the occurrence of the generalized rash might have caused a fatality. The occurrence of localized exfoliative dermatitis in other cases has emphatically illustrated the dangers of local penicillin. One patient had an exfoliation of the skin of the entire external ear canal and pinna, after treatment of a chronic suppurative otitis media, with purulent drainage from a tympanic perforation by installation of penicillin solution into the ear. The impression gained from personal experience is that the local administration of penicillin in the region of the head and neck causes a higher rate of sensitization and is definitely contraindicated. With

the possibility of severe and potentially fatal reactions and the chance that sensitivity induced by local therapy may prevent parenteral penicillin therapy when a severe systemic infection later occurs, it seems best to discontinue local penicillin therapy entirely. The availability of other suitable local therapeutic agents, such as ammoniated mercury and tyrothricin, and the superiority or equality of parenterally administered penicillin in the treatment of superficial cutaneous infections are further facts to discourage the dangerous practice of using penicillin locally.

### SUMMARY

A case of generalized exfoliative dermatitis due to sensitivity to penicillin is presented.

Penicillin ointment is contraindicated in the treatment of skin lesions because of the reactions dangerous to life that may occur during the treatment of an innocuous condition and also because systemic sensitization may prevent later parenteral use of

penicillin when it is needed to combat a severe systemic infection.

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## MEDICAL PROGRESS

### REGIONAL ANESTHESIA\*

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THE war and the following years witnessed a widespread increase of interest in regional anesthesia. This was a natural sequence to the emphasis placed upon the role of anesthesia in war surgery. Many of the young physicians who received training in anesthesiology during the war have chosen to complete their training in that specialty. Their enthusiasm has added to the magnitude of experimental and clinical investigation of the postwar period. Differential spinal block has furnished new evidence of the mechanism of nerve block. New diagnostic and therapeutic sympathetic blocks have broadened the field of the anesthesiologist. Segmental spinal anesthesia invites further investigation into the potentialities of decreasing the concentration of a spinal anesthetic agent. The synthesis of morphine-like compounds promises a brighter future for better premedication and post-operative relief of pain. The development of new and the modification of older techniques in the past few years have aided in the personalization of the anesthesia to the individual patient.

### DIFFERENTIAL SPINAL BLOCK

It has long been known that anesthetic agents introduced into the subarachnoid space did not equally affect all nerve components. New evidence that the smaller, nonmyelinated fibers are blocked first is presented in the work of Sarnoff and Arrowood<sup>1-3</sup> on "differential spinal block." They employed the continuous spinal technic with 0.2 per cent procaine hydrochloride solution in an attempt to produce differential block of the sympathetic fibers. Skin-temperature readings were used as a measure of sympathetic activity. Their results indicated that sympathetic preganglionic vasomotor and adrenergic fibers were blocked at or about the same time as the fibers concerned with the appreciation of pinprick. These fibers were blocked without impairment of the modalities of touch, deep pressure, position sense or vibratory sense and with no loss of motor power. A further observation was that position sense and the stretch reflexes are mediated by separate groups of fibers. This was shown by a loss of abdominal, patellar and Achilles-tendon reflexes when position sense was still appreciable.

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Jackson<sup>40</sup> described another aliphatic amine similar to oenethyl except for an extra methyl and hydroxyl radical. This drug, termed EA-83, is readily absorbed from the gastrointestinal tract in dogs, but as yet no clinical investigation has been undertaken.

### *Morphine and Morphine-like Drugs*

Drew, Dripps and Comroe<sup>41</sup> studied the effects of morphine upon the circulatory changes in man after position change. They found that movement of a "morphinized" patient from the supine to the sitting or semierect position may be followed by vascular collapse. Powers<sup>42</sup> re-emphasized the addiction properties of demerol, and Robbins<sup>43</sup> demonstrated that cyclopropane-induced cardiac irregularities after morphine premedication are not seen in the dog when demerol is used. Foster and Carman<sup>44</sup> tested demerol and other piperidine derivatives on the rat and reported that some are deserving of clinical trial.

When the United States Government study commissions went to Germany after World War II, they found a group of compounds, prepared by German chemists, that exhibited hypnotic action. One of these synthetic hypnotics — No. 10820, or dolophine — has been thoroughly studied by the Lilly research group and named methadon (6-dimethylamino-4,4-diphenyl-heptanone-3). C. C. Scott and Chen<sup>45-47</sup> found that methadon has an analgesic effect as powerful as morphine. In addition, it depressed respiration, caused cardiac slowing and produced a slight to moderate fall in blood pressure, but there was no depression of salivary secretion and it only occasionally caused nausea and vomiting. An associated depression of the cough reflex and parasympathomimetic stimulation of the small bowel were noted. Isbell<sup>48</sup> used methadon in the treatment of morphine addiction and reported the development of tolerance and addiction to methadon. With methadon, however, withdrawal symptoms were not nearly so severe as those with morphine, and he advocated substitution of methadon for morphine before withdrawal in addicts. W. W. Scott et al.<sup>49</sup> observed no euphoria when methadon was given clinically for preanesthetic medication and postoperative relief of pain.

### *Local Anesthetic Agents*

An increasing number of compounds are being investigated from the standpoint of their potential anesthetic properties. Krop<sup>50</sup> studied pyridium ( $\beta$ -phenylazo  $\alpha$ - $\alpha'$  diamino pyridine monohydrochloride) and re-emphasized that it might be useful as a topical anesthetic in the bladder and urethra. Kuna and Seeler<sup>51</sup> studied the anesthetic properties of a large group of alkyl amino alcohol esters and reported that several hold promise for infiltration anesthesia. One in particular in this group, 2-cyclopentyl amino-1-propyl p-aminobenzoate hydrochloride, might prove valuable for topical as well as for

infiltration anesthesia. Ramsey and Haag<sup>52</sup> reported a series of aryl-urethanes that possessed anesthetic activity greater than that of cocaine when instilled in the rabbit eye.

Combes et al.<sup>53</sup> advocated the use of topical anesthetic agents in ointment bases for the treatment of burns and cutaneous ulcers. They claimed that this procedure promoted rapid healing and soft scar formation by lessening the vasodilatation, edema and muscle spasm that accompanies the pain of the acute lesion.

### OBSTETRIC ANESTHESIA

Spinal analgesia for obstetric delivery is enjoying greater popularity than ever before. Weaver and his co-workers,<sup>54</sup> Turner<sup>55</sup> and Marcus and his associates<sup>56</sup> reported on large series with excellent results. Cullen and Griffith<sup>57</sup> compared post-partum results of spinal and gas anesthesia for vaginal delivery. The evidence in their study was in favor of spinal anesthesia, except that headaches were severer, although the incidence of headache in the two groups was the same. Weintraub et al.<sup>58</sup> compared the incidence of postlaparotomy spinal headache in cesarean section and various gynecologic operations with the incidence in vaginal delivery under spinal anesthesia. The incidence of headache following spinal anesthesia was much higher in the last group than in the first two groups, averaging 15 per cent in 300 patients. In the vaginal-delivery group 50 per cent of the patients who complained of headache exhibited orthostatic hypotension or tachycardia or both. These investigators found that the application of a tight abdominal binder post partum gave complete or almost complete relief in 90 per cent of the patients with headache.

Resnick,<sup>59</sup> of Great Britain, weighted nupercaine with glucose for use in obstetric delivery. Parmley and Adriani,<sup>60</sup> in this country, popularized "saddle block" anesthesia with heavy nupercaine for vaginal delivery.

Caudal and continuous caudal anesthesia are still enjoying great popularity in certain communities. Brown et al.<sup>61</sup> tested various concentrations of pontocaine in physiologic saline solution with epinephrine (dilution of 1:200,000) for duration of effect. Using continuous caudal anesthesia, they found that pontocaine, 0.15 per cent, proved the most effective.

A review of the technic of pudendal-nerve block is reported by Eisaman and McHenry.<sup>62</sup>

### TECHNICS

The increasing number of qualified anesthesiologists has brought reports of new technics in regional anesthesia. Adriani and Roman-Vega<sup>63</sup> used saddle-block anesthesia with a weighted solution of nupercaine. They employed the sitting position for injection and produced anesthesia in the anoperineal region without motor block of the lower extremities.

A method of continuous brachial-plexus block utilizing a blunt needle with a cork stabilizer was presented by Ansbro<sup>41</sup>. Kersbner and Shapiro<sup>42</sup> reported a technic of interlaminar approach for spinal subarachnoid puncture as an alternative to the conventional interspinous method.

Lund and Rumball<sup>43</sup> dissolved pontocaine crystals in distilled water to make a 0.1 per cent hypobasic solution in a controlled series and concluded that the ephedrine decreased the dosage by approximately a third but did not appreciably increase the length of its effect. Ruben<sup>44</sup> added ephedrine to pontocaine-glucose and made use of the prolonged lateral position to obtain increased length of anesthesia for unilateral orthopedic procedures on the lower extremity.

Roman-Vega and Adriani<sup>45</sup> reported further on the use of weighted nupercaine with gravity control for general abdominal surgery. Nitikman<sup>46</sup> outlined another formula for nupercaine dosage in nucleopulposus surgery.

Two articles on the status of epidural anesthesia are in the recent literature, both from the southern continents where this technic apparently enjoys much greater popularity than it does in this country. Lima<sup>47</sup> reported from Brazil, and van Hoogstraten<sup>48</sup> from the Union of South Africa.

McCann<sup>49-51</sup> has made use of supplementary nerve block with pentothal sodium anesthesia for general surgery. Relaxation for abdominal surgery was achieved by transincisional blocking of the intercostal nerves within the rectus sheath. He prevented deep reflex stimulation of respiration by anterior splanchnic and mesenteric block in intra-abdominal surgical procedures. Transincisional intercostal block was done during radical mastectomies. The quantity of pentothal necessary for any general surgical operation was reduced by almost 50 per cent when such supplementary nerve block was employed.

Ingram<sup>52</sup> et al<sup>53</sup> found that local reduction in cutaneous temperature facilitated the introduction of needles through the skin of children for the purpose of medication or venipuncture. They used an insulated, ice-filled copper tube, which maintained a constant temperature for several hours. Application for a few seconds produced sufficient cooling for painless skin puncture.

### Complications

Every method of effecting anesthesia for surgical procedures over an extended period of use has been accompanied by certain complications. Regional anesthesia, however, has its specific category of complications, chief among which are nerve paralyses and subarachnoid sepsis. Nicholson and Eversole<sup>54</sup> recently presented a review on the neurologic com-

plications of spinal anesthesia. Steinberg and Bishop<sup>55</sup> and Fairclough<sup>56</sup> reviewed the pathogenesis of abducens-nerve palsy after spinal anesthesia, and Rose and Pritzker<sup>57</sup> reported a recent case. Evans<sup>58</sup> collected a number of cases of meningitis following spinal anesthesia and outlined a technic for prevention. Kennedy et al<sup>59</sup> described 3 cases of fibrinous arachnoiditis after spinal anesthesia. Chivers<sup>60</sup> reported that the incidence of pneumothorax with intercostal nerve block was 19 per cent.

### REPLACEMENT THERAPY

That a real need exists for better methods of evaluating the effectiveness of modern preoperative preparation of the poor-risk surgical patient is keenly appreciated by both the surgeon and the anesthetist. Too often, a patient who is considered adequately prepared shows signs of shock in the operating room or develops a serious postoperative surgical complication. Recently, attention has been directed to the decreased blood volume in these chronically ill patients. Lyons et al<sup>61-63</sup> introduced the term "chronic shock" to describe this condition. The complete syndrome consists of weight loss, decreased blood volume, decreased blood protein and increased interstitial fluid volume. The authors showed that weight loss was correlated with reduced total mass of blood proteins without significant alteration of blood protein concentration. Lowering of the total hemoglobin mass, as in chronic bleeding, leads to the loss of plasma from the vascular bed to the interstitial fluid compartment. A reduction in plasma volume, as well as a loss of total hemoglobin, may mask deficiencies in the total mass of blood proteins. Ordinary methods of blood determinations, they contend, will then fail to show the reduction of blood volume and the attendant increased susceptibility to shock. Lyons et al<sup>64</sup> stated that corrective therapy consisted of whole-blood transfusion. In their studies adequate correction of chronic shock necessitated an average of 2700 cc of blood in the preoperative period. After such treatment the plasma-volume increase approximates but rarely equals or exceeds the gain in erythrocyte volume. Consequently, the restoration of the hematocrit value to 50 per cent was advocated as an index of adequate therapy. A fundamental disturbance in hemoglobin metabolism was shown to be present in patients suffering from cancer.

Davidson and his associates<sup>65</sup> studied blood changes in patients with acute medical illnesses. They found that patients exhibiting peripheral vascular collapse had hyperglycemia, lactic acidemia and a decrease in the bicarbonate reserve. There was also usually a lengthening of the prothrombin time and an elevation of the icteric index.

Scheinberg et al<sup>66</sup> reported on homologous serum jaundice and warned against injudicious use of blood plasma from pooled lots.



## SUMMARY

The medical literature since World War II has introduced many new advances in regional anesthesia. Segmental spinal anesthesia and the addition of vasopressor drugs to agents used for spinal anesthesia are advocated as aids in decreasing the concentration and total amount of spinal drug necessary. Better control of the hypotension seen with spinal anesthesia is offered by new vasopressor drugs. The investigation of synthetic hypnotics gives promise of better preoperative and postoperative management of the surgical patient's apprehension and pain. Sympathetic-nerve block has proved an effective therapeutic agent in many disorders heretofore uncontrollable. The use of weighted spinal-anesthetic solutions for vaginal delivery offers a safer agent for obstetric anesthesia, and finally, the recognition of the serious depletion of whole blood volume in chronically ill patients throws new light on the preoperative preparation of this group.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 34191

#### PRESENTATION OF CASE

**First admission.** A twenty-seven-year-old housewife entered the hospital because of shortness of breath.

This symptom had bothered her as long as she could remember. She had always restricted her activities and found running impossible. She slept propped up on at least two pillows and had often been aware that the heart beat forcefully. Dyspnea and orthopnea became gradually severer during the two years before admission, and several new symptoms developed. These consisted of a dull ache to the left of the sternum, at first only after eating and then almost constantly, ankle swelling after standing for any length of time and cyanosis of the face, lips and fingernails aggravated by exertion. Two months before admission a new type of chest pain was noted, a constricting sensation beneath the sternum, associated with exertion, disappearing on rest and nonradiating. During the month before admission the patient was confined to bed

with a respiratory infection. She entered the hospital because of failure to improve.

There was no history of rheumatic fever or other heart disease. Upper respiratory infections were frequent during the winter prior to admission, and the patient was bothered by a chronic, dry cough. There was no history of hemoptysis, night sweats or pleural pain. Seventeen years before admission she had entered the hospital because of polyuria and polydipsia. Physical examination was essentially negative. The chest was clear, and the heart sounds were unremarkable except that the pulmonary second sound was split and the same double sound was heard at the apex but to a less marked degree. No murmurs were heard. Examination of the blood was negative. The urine was not remarkable, except that the specific gravity seldom exceeded 1.002. A diagnosis of diabetes insipidus was made, and the patient was given surgical pituitrin, which controlled the symptoms. At home she continued the drug, two or three injections a day for fifteen years until two years before the present admission, when this treatment was stopped and the symptoms did not recur. The onset of catamenia had been very irregular. She had been married twice but had never become pregnant.

Physical examination showed an intensely cyanotic, rather obese woman lying propped up in bed. The veins of the fundi were tortuous and engorged, although the neck veins were not distended. The chest was clear to percussion and auscultation. The left border of cardiac dullness was at the midclavicular line, the right border was not percussible. The most forceful impulse was in the third and fourth left interspaces, it was much stronger than the apical beat. The pulmonary second sound was very loud and the pulmonary first sound

moderately so, and the other heart sounds were distant. There was a soft, short diastolic murmur best heard in the third left interspace. The abdomen was obese and showed striae, and palpation revealed tenderness in the right lower quadrant. No organs or masses were felt. There were clubbing and cyanosis of the fingers and toes.

The temperature and pulse were normal. The respirations were 40. The blood pressure was 108 systolic, 80 diastolic.

The urine gave a +++ test for albumin and had a specific gravity of 1.006, the sediment contained epithelial cells. The red-cell count was 8,450,000, the hemoglobin 18.5 gm, and the white-cell count 9550. The fasting blood sugar, the nonprotein nitrogen, the carbon dioxide, the total protein, the sodium and the chloride were all within normal limits. The venous pressure was equivalent to 120 mm of water, the circulation time was 8 seconds with ether and 30 seconds with decholin. An x-ray film of the chest showed enlargement in the region of the left auricle and ventricle. The pulmonary artery and lung roots were prominent. An electrocardiogram revealed sinus rhythm, with a rate of 85, and a PR interval of 0.24 second, a QRS complex of 0.09 second, normal voltage, right-axis deviation, a slurred R wave in Lead 2, sagging ST segments in Leads 2 and 3, flat T waves in Leads 1 and 2, a very low T wave in Lead 3 and sagging ST segments in Leads CF<sub>1</sub>, CF<sub>4</sub> and CF<sub>6</sub>, with a prominent S wave in Lead CF<sub>1</sub> and inverted CF<sub>1</sub>, CF<sub>4</sub> and CF<sub>6</sub>. The patient improved on small venesections, digitalis and ammonium chloride. She was discharged on a low-sodium diet to be followed in the Cardiac Clinic.

*Second admission* (two months later). The patient did well on markedly limited activity until two months later, when she had an attack of breathlessness and substernal pain and was readmitted to the Emergency Ward. The physical findings had not changed. The diastolic murmur was described as a rumble, and an early diastolic blow was heard in the second left interspace. She improved on aminophyllin and was discharged after a two-day stay.

*Third admission* (five months later). During the period after discharge she was treated with venesection on several occasions, which lessened the symptoms. During the five days before re-entry she had three attacks of severe, stabbing pain in the left breast. Nausea, vomiting and great anxiety were also prominent symptoms.

Physical examination revealed an extremely agitated, cyanotic woman, lying flat on a stretcher. The pulse rate was 100, and the respirations 40. The blood pressure was 80 systolic, 60 diastolic. There was no venous distention with the patient sitting up. The chest was clear, and the heart unchanged. The liver edge was not felt. Five hours later the patient was examined by a consultant,

who found in addition to the above findings a protodiastolic gallop and many dry, crepitant rales. Pressure on the right upper quadrant did not distend the cervical veins or reveal pulsations, but while this procedure was being done the patient suddenly stopped breathing, became pulseless and died.

#### DIFFERENTIAL DIAGNOSIS

DR HOWARD B. SPRAGUE: May we see the x-ray films?

DR STANLEY M. WYMAN: The heart shadow is enlarged as described in the record. The left auricle appears to have displaced the left main-stem bronchus upward and to have narrowed it slightly. The enlargement of the left auricle is seen in the oblique view, I do not believe that I can say whether the enlargement of the ventricles is to the left or the right from the films alone. The heart comes far forward to the chest wall, strongly suggesting that the right ventricle might be large, and far posteriorly, which makes one question the left ventricle also. The main pulmonary artery is strikingly prominent in the anteroposterior projection, and the left and right main pulmonary arteries are more prominent than usual. The aorta is small. The lung fields are essentially clear. There is no evidence of pleural fluid.

DR SPRAGUE: There is no pulmonary lesion that you can find, except vascular?

DR WYMAN: I see no localized pulmonary disease. I cannot detect any intracardiac calcification on the films. I do not know about fluoroscopy.

DR SPRAGUE: The right-axis deviation in the electrocardiogram is an important finding. It tends to contradict the observation of the left ventricular enlargement by x-ray examination.

I am going to start by saying that this is a case of pulmonary hypertension and see where we can go from there. The chronology is important. This woman had been dyspneic all her life, which is in favor of some type of congenital lesion, cardiac or pulmonary. At the age of ten years the examination showed no cyanosis or clubbing, no heart murmurs and no other cardiac abnormalities, except for a split second sound at the pulmonary area, and a negative blood examination. At the age of twenty-five dyspnea and orthopnea had increased and a dull ache developed at the left of the sternum, with ankle swelling on standing, cyanosis of the face, lips and fingernails, worse on exertion, and chronic dry cough. At twenty-seven years of age the patient entered the hospital, and examination showed obesity, intense cyanosis, a forceful impulse in the left third and fourth spaces, a loud pulmonic second sound, a soft diastolic murmur along the left upper sternal border and clubbing of the fingers and toes. Is there any note about the degree of clubbing?

DR. TRACY B. MALLORY: It was rather severe clubbing.

DR. SPRAGUE: The significant laboratory findings are a red-cell count of 8,500,000, with a hemoglobin of 18.5 gm., somewhat increased venous pressure with normal arm-to-lung but prolonged arm-to-tongue circulation time. Of course this chronology rules out at once the congenital cardiac conditions associated with cyanosis and death in early life because this is primarily a patient with delayed cyanosis, and for that reason I have to assume that there was some change in the pressure relations in the circulation if we are going to invoke a veno-arterial shunt. There may previously have been an arteriovenous shunt, but whether or not we invoke this change in circulatory dynamics the evidence does point toward changes in the pulmonary circulation as being most important. If we assume that there was a congenital cardiac condition, what are the arteriovenous shunts not associated with cyanosis in early life, that may become veno-arterial shunts if there is a change in the pressure relations? One should mention interauricular septal defect, with or without mitral stenosis congenita or acquired—a Lutembacher syndrome, a high interventricular septal defect, patent ductus arteriosus, and, finally, Eisenmenger's complex. Regarding the pulmonary conditions, if we assume that we are dealing primarily with a pulmonary situation, with secondary cardiac changes of cor pulmonale, there may have been congenital anomaly, hypoplasia of the vascular tree or a change of some sort in the endothelium of the arterioles or capillaries. There may have been endarteritis or possibly secondary changes in the pulmonary circuit due to prolonged arteriovenous communication as in some cases of patent ductus, which transposes the systemic pressure to the pulmonary side and results in changes in the lung vessels, causing delayed increase in pulmonary blood pressure. Finally, there are the unexplained changes in the lung of the Eisenmenger complex. In that condition there are a dextroposed aorta, a high interventricular septal defect and a large pulmonary artery as contrasted with the small pulmonary artery of the tetralogy of Fallot. In the Eisenmenger complex there is no obstruction in the outflow tract of the right side of the heart, but increased peripheral resistance in the lung, and little or no cyanosis, or delayed cyanosis. I think this development of heart symptoms with severe compensatory polycythemia and chest pain can be interpreted under the term of "angina hypercyanotica," which is described in conditions of high pulmonary pressure and polycythemia although in this case I cannot rule out some degree of coronary insufficiency. Against interventricular septal defect, with or without mitral stenosis, clinically, is the fact that this woman was obese. These patients tend to be of slight build. There was not the striking increase

in the pulmonary vascular markings typically associated with an interauricular septal defect, in which there is tremendous increase in the pulmonary flow. Furthermore, in interauricular septal defect the cyanosis—the "cyanose tardive" of the French—is not of long enough duration before death to be associated ordinarily with clubbing of the fingers. In interauricular septal defects one frequently sees auricular fibrillation, and, furthermore, there was no history in this case of rheumatic infection, which patients with interauricular septal defect are very prone to have.

As against uncomplicated high interventricular septal defect, I am worried about the absence of a systolic murmur because the condition is clinically associated with a loud systolic murmur and thrill. Against patent ductus arteriosus, again, is the absence of anything characteristic of the continuous murmur of patent ductus arteriosus. Against the Eisenmenger complex again there is no evidence of interventricular septal defect. There was no murmur, and although a soft early diastolic murmur had developed along the left sternal border, I am more willing to call that a functional murmur, a Graham-Steell murmur, rather than that of aortic regurgitation, which may be found with the Eisenmenger complex, because the aortic valve may be involved in the anomaly high up in the septum.

The evidence for primary pulmonary disease of the small arterioles is that the findings were those of dyspnea without diagnostic murmurs, and I might be inclined to think that we are dealing with a congenital vascular anomaly of the pulmonary bed. I believe that with such a condition the patient would not have gone so long as this without cyanosis and failure.

The lack of support for the diagnosis of veno-arterial shunt is the prolonged arm-to-tongue time. If something is injected into the vein and goes from the right side of the heart immediately over to the aorta, there should be shortening of the circulation time to the tongue. On the other hand, there may be such a slight venoarterial shunt that that is not good evidence. In this sort of situation Taussig<sup>1</sup> has recently emphasized the trial of inhalation of oxygen as being diagnostically valuable because if the cyanosis is due to a pulmonary condition, it may disappear. But in the Eisenmenger complex the oxygen saturation of the arterial blood will not be normal because there is still some degree of shunt of venous blood between the right ventricle and the aorta.

The events in the last seven months of the patient's history are attacks of breathlessness and substernal pain and what is described as a diastolic rumble. I do not know whether that has been added to make one think this was a Lutembacher syndrome with mitral stenosis, or whether it was an interpretation of one observer of what was later

called a gallop rhythm, perhaps gallop rhythm of the right ventricle. The final severe stabbing pain in the left breast, the fall in pressure, the absence of venous distention and the sudden death could have been due to either coronary-artery or pulmonary failure.

In summarizing this rather complicated situation, what do we have as possibilities? I should say primary pulmonary vascular anomaly that the patient had had all her life. There is no reason to consider that she represents the type of patient we have seen in these sessions in whom there has been pulmonary endarteritis or an obstruction of the finer vascular radicles. There are cases of multiple emboli, such as those described by Castleman and Bland<sup>2</sup>. The symptom of dyspnea in this case, however, was present all her life. Any arteriovenous shunt, I think, may well lead to greater pressure strain on the lesser circulation relative to that on the systemic. Volume strain is usually tolerated better than pressure strain on the pulmonary circuit. However, when these conditions exist more changes in the pulmonary vessels may ensue. These, in turn, increase the pulmonary pressure and result in reversal of an arteriovenous shunt, as in interauricular or interventricular septal defect, or even patent ductus arteriosus. That possibility has been advanced recently as another reason for ligation of patent ductus arteriosus.

I do not believe that we are dealing with idiopathic pulmonary fibrosis with cor pulmonale, but I confess that we have little evidence beyond the long history and delayed cyanosis to support a diagnosis of Eisenmenger's complex, mostly because of the absence of murmur. Yet we have certain cases of tetralogy of Fallot in which there is also an interventricular septal defect without a systolic murmur. I think that can be explained only by the fact that there may be only a small pressure gradient between the right and left ventricles, and murmurs are suppressed by increased blood viscosity from the polycythemia.

That brings us to what happens in the lung in the Eisenmenger complex. With a large pulmonary artery and an interventricular septal defect one would expect that the blood from the right side of the heart would readily pass into the pulmonary artery and not go into the left side of the heart and aorta to cause cyanosis. That is what happens in early life, but for some reason this increase in peripheral resistance in the lung occurs and cyanosis develops, mainly because of faulty oxygenation in the lung and also because of venous admixture through the ventricular septal defect. I am therefore going to vote for a combination consisting of a dextroposition of the aorta, explaining perhaps the small aortic shadow, the large pulmonary artery and a high interventricular septal defect. Thrombosis probably occurred in the pulmonary vessels. I cannot say just what may be found

anatomically in these vessels, but there will be some type of abnormality. The patient probably had some coronary insufficiency, either from anoxemia and increased blood viscosity, in addition to what was a real anemia after the venesections, or from functional pulmonary-valve regurgitation, which the pathologist will probably not be able to prove.

DR MALLORY I take it you are not interested in the diabetes insipidus?

DR SPRAGUE It did bother me, but I cannot fit it in except as a manifestation of another congenital anomaly, although we have no history of any familial incidence.

DR JOSEPH AUB I am interested by the fact that when the patient was ten years old there was no suggestion of cyanosis.

DR SPRAGUE She had an increased pulmonary second sound and was unable to breathe comfortably.

DR AUB The same thing that was bothering the pulmonary vessels may have bothered the pituitary vessels when she was ten. How is that?

DR SPRAGUE Good.

DR AUB Then the whole thing would have been vascular.

DR SPRAGUE She pulled through the diabetes insipidus.

DR AUB. She had extensive circulation.

A PHYSICIAN How do you explain the increased PR interval?

DR SPRAGUE I think that the increased PR interval was nonspecific.

#### CLINICAL DIAGNOSES

Congenital heart disease, incompletely diagnosed  
Pulmonary endarteritis?

#### DR SPRAGUE'S DIAGNOSES

Interventricular septal defect.  
Dextroposition of aorta.  
Thrombosis of pulmonary vessels, probable

#### ANATOMICAL DIAGNOSES

*Pulmonary fibrosis and emphysema, with slight bronchiectasis*  
*Cor pulmonale*  
Hydrothorax, bilateral  
Chronic passive congestion  
Pulmonary arteriosclerosis, slight  
Hyperplasia of bone marrow  
Adenoma of thyroid gland

#### PATHOLOGICAL DISCUSSION

DR MALLORY I have to present my evidence visually—otherwise you will not believe me. We found a marked cor pulmonale. The heart weighed 450 gm. The right ventricle was almost as large as the left, measuring 12 mm in thickness. There were no congenital abnormalities of any sort.

The lungs, in contrast, showed a diffuse fibrosis and emphysema (Fig 1). Here is a focal granuloma in the lung with numerous foreign-body giant cells, faintly suggestive of sarcoid (Fig 2). Here is an area of bronchiectasis surrounded by rather extensive bands of fibrosis. I think this case is one of true cor pulmonale. What the explanation of the pulmonary changes remains very much more of a problem. The patient was very young to have a severe emphysema. When we do see it in young people it is usually associated with evidence of some destructive fibrotic process that has occurred in the past. One group of such cases that we have

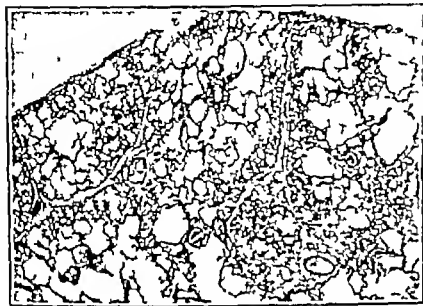


FIGURE 1

recently been interested in here shows multiple sarcoid-like lesions throughout the lung. The evidence for that is minimal in the case under discussion. There were a small number of lesions such as the one I showed that suggested it, but if there ever was an extensive process of that sort, it had almost completely healed. It is also rather mysterious that there was no x-ray evidence of extensive pulmonary changes. The pulmonary vessels showed a few patches of atheroma but no narrowing of the vascular lumens. The bone marrow showed red-cell hyperplasia due to anoxemia, and there was a small coincidental adenoma of the thyroid gland.

DR. SPRAGUE: I have seen that and have been impressed with what we call idiopathic pulmonary fibrosis and emphysema, with absolutely normal chest films. It may be that the changes in the lung were on a congenital basis.

DR. MALLORY: No, I think they were acquired

DR. SPRAGUE: As long ago as the patient could remember?

DR. MALLORY: Yes.

DR. AUB: Then how about the pituitary body?

DR. MALLORY: It showed extensive atrophy of the posterior lobe, quite characteristic of what is



FIGURE 2

seen in diabetes insipidus. Why she should recover I cannot understand, because she had almost no posterior lobe left.

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#### CASE 34192

##### PRESENTATION OF CASE

A fifty-two-year-old nulliparous housewife entered the hospital because of weakness and fatigability, pain in the left arm and leg, tinnitus, deafness and difficulty in swallowing and talking.

Fatigue and dyspnea were first noted two years before entry and became progressively worse. For several months the patient was able to perform only a minimal amount of housework. During the same period she had almost continuous severe steady pain in the left arm and "over the breast" associated with a sensation of coldness. Four months before admission there was a rapid change in the character and severity of the pain. The entire left side of the body became involved in an agonizing pain, constantly running up and down the left side of the body. Coincident with this

change in the pain there was a constant ringing in both ears, and three months later hearing became impaired. The tinnitus gradually lessened and on admission was entirely absent. There had not been any vertigo or nausea. During the few weeks before admission, while in another hospital, the patient developed a rapidly progressive weakness of the right facial nerve and difficulty in swallowing and talking. While there she required tube and intravenous feedings.

Physical examination revealed a thin, debilitated and dehydrated woman, who was alert and oriented. The heart, lungs and abdomen were normal. All four extremities could be moved equally, though feebly, and she could walk with assistance. The fundi were normal. The right pupil was 3 mm and the left 2 mm in diameter, both reacted to light. There was no nystagmus. There was palsy of the left external rectus and superior oblique muscles. The left palpebral fissure was narrower than the right. There was bilateral paralysis of masseter and pterygoid muscles and sensory loss in the left facial nerve, with a diminished corneal reflex and conjunctivitis of the left eye. Motion in the right lower part of the face was absent, and on the left was limited to a feeble upward twitch of the corner of the mouth. The sense of taste was lost. There was gross diminution of hearing bilaterally. Bone conduction was greater than air conduction. The Weber test was negative. The gag reflex was absent, and the patient was unable to swallow. There were marked weakness and slight atrophy of the tongue. The deep tendon reflexes of the arms were hyperactive, more so on the left. They were absent in the legs. The abdominal reflexes were absent, and the plantar reflexes were normal. Stereognosis and vibration sense were normal bilaterally.

The temperature was 98°F, the pulse 90 (equal and synchronous), and the respirations 25. The blood pressure was 178 systolic, 110 diastolic.

Examination of the blood at the other hospital just before admission disclosed a red-cell count of 5,000,000, with a hemoglobin of 13.2 gm, and a white-cell count of 6400, with 68 per cent neutrophils. The urine was normal. The blood sugar was 130 mg, and the nonprotein nitrogen 33 mg per 100 cc. The sedimentation rate was 85 mm per hour. A lumbar puncture done three weeks before entry showed an initial pressure equivalent to 200 mm of water, which rose to 240 mm on jugular compression and fell to 120 mm after re-

moval of slightly xanthochromic fluid, which contained 5 lymphocytes per cubic millimeter and gave a total protein of 250 mg per 100 cc with a +++ Pandy test. Ten days later the initial spinal-fluid pressure was equivalent to 290 mm of water, with a protein of 500 mg per 100 cc, a ++++ Pandy test and 18 lymphocytes per cubic millimeter.

On the first night the patient became very noisy and apprehensive and was given paraldehyde by rectum. A few hours later the respirations suddenly fell to 6 per minute. Oxygen was given by a Boothby mask. The temperature remained normal. The patient died in respiratory failure twenty-four hours after admission.

### DIFFERENTIAL DIAGNOSIS

DR. ROY L. SWANK\* Stereognosis and vibration sense were normal bilaterally, but we are not told about other sensations. Should we assume that they were normal?

DR. CHARLES S. KUBIK The sensations of touch and pinprick were said to be normal.

DR. SWANK I believe that the patient had a lesion in the brain stem or the cranial nerves emanating from it, or both, from the level of the fourth or fifth to the twelfth cranial nerve. This was certainly not a typical acoustic neuroma, although it may have been very atypical or bilateral. There are certain features that, in my mind, rule out these diagnoses: the absence of nystagmus, the absence of history of staggering or ataxia, the absence of papilledema and the order in which the symptoms developed. I also feel the same about other single tumors outside the medulla and pons in the posterior fossa. I am unable to make such a diagnosis.

Other extramedullary conditions are suggested by the fact that the patient experienced vertigo and dyspnea two years before entry, by the findings relative to the ear and by the sedimentation rate of 85 mm per hour. The white-cell count was normal, however, and there was no significant increase in neutrophils. I wonder if we are dealing with a chronic basilar meningitis. Tuberculosis would have to be thought of. Could it have been present for two years? There is no history of cough, and no report of x-ray studies. It seems unlikely that active tuberculosis was present so long. There is no history of treatment with streptomycin, which might have altered the story. I am inclined to

\*Assistant visiting neurologist, Boston City Hospital.

discard this diagnosis. Was an x-ray film taken of the chest?

DR. KUBIK: X-ray studies were not done in this hospital.

DR. SWANK: Chronic, nonspecific, basilar meningitis associated with chronic middle-ear disease is another possibility. One would have to assume that the middle-ear disease was bilateral. I consider this a difficult diagnosis to arrive at from the information at hand.

This brings me to two diagnoses, which I shall consider seriously. The first is a glioma of the pons. This is a slowly progressive condition involving the cranial nerves late and producing increase in cranial pressure late, if at all. I believe that this diagnosis is possible. The few cases of this condition that I have seen have had marked ataxia and nystagmus. I see no reason why this condition might not pick out other systems in the brain stem, however. A glioma of the pons must extend from the lower end of the medulla to the upper pons and probably the lower midportion of the brain on the left. There are several things that are difficult to explain on this basis. It leaves me unable to account for the findings relative to the ear. Bone conduction was greater than air conduction. To explain this I assume that the patient was grossly deaf and was not hearing the tuning fork, but feeling it. Also, unnnit of the prominence described in this case is unusual in intramedullary lesions. The spinal-fluid protein was markedly elevated, much more than it usually is in glioma of the pons, I shall assume that a block had occurred late in the disease and that the elevated protein content was a result of the block. Had the puncture been done some months earlier, normal protein might have been present.

Lastly, I think it is necessary to consider a malignant tumor with metastases. Metastases to the dura and to the sheaths of the cranial nerves could produce the clinical picture under discussion. Symptoms due to this lesion may be difficult to understand even after post-mortem examination. If the history is correct, one must assume that the metastases were present for two years and also that the primary site, most likely the lungs, was overlooked. It seems to me that this history was very long for dural metastases. I would consider metastatic carcinoma an attractive diagnosis but not possible to arrive at under the circumstances.

As a most likely diagnosis in this case I have to fall back on tumor within the pons and medulla, a glioma. I am not happy about it, but I believe that it has the fewest objectionable features.

DR. AUGUSTUS ROSE: I am interested in the severe pain on the left side of the body, and I wonder if Dr. Swank would assume that that was "thalamic" pain.

DR. SWANK: That has been seriously considered because it is difficult to explain the pain on the basis of a lesion in the medulla or pons. If one assumes that it was thalamic, one also assumes that there were two separate lesions and that the third-nerve nucleus was missed. I believe that this is unlikely. The smaller pupil and the drooped lid might indicate third-nerve involvement. I consider it more likely that this was due to a lesion within the brain stem producing a mild Horner's syndrome. Conditions such as syringomyelia are apt to cause pain within the spinal cord, and perhaps a similar mechanism operated in the brain stem in this case.

#### CLINICAL DIAGNOSIS

Amiotrophic lateral sclerosis

#### DR. SWANK'S DIAGNOSIS

Glioma of pons and medulla

#### ANATOMICAL DIAGNOSIS

*Metastatic adenocarcinoma, primary site undiscov-  
ered*

#### PATHOLOGICAL DISCUSSION

DR. KUBIK: I should like to say that this is probably one of the most difficult neurologic cases that has been presented here. Dr. Swank came very close to the diagnosis when he suggested the possibility of metastases. There was an unusual type of metastasis, consisting of carcinomatous invasion of the subarachnoid space with involvement of the cranial and spinal nerves. The metastatic tumor was made up of columnar cells, which formed perfect tubules and also spread out in a single layer, covering the inner surface of the arachnoid membrane, blood vessels and cranial and spinal nerves in a most unusual and fascinating way. There was invasion of the cranial and spinal nerves and slight subpial invasion of the cord and medulla. In spite of a complete autopsy, no primary tumor was found. I cannot believe, however, that a neoplasm of this type could have been primary in the central nervous system, and I assume that the primary lesion was so small that it was overlooked. We have had two or three other cases of metastatic carcinomatosis of the subarachnoid space, though none with such extensive paralyzes as this. In at least one case there were cells in the cerebrospinal fluid, and a clinical diagnosis of tuberculous meningitis had been made.



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As a most likely diagnosis in this case I have to fall back on tumor within the pons and medulla, a glioma. I am not happy about it, but I believe that it has the fewest objectionable features.

DR AUGUSTUS ROSE I am interested in the severe pain on the left side of the body, and I wonder if Dr Swank would assume that that was "thalamic" pain.

DR SWANK That has been seriously considered because it is difficult to explain the pain on the basis of a lesion in the medulla or pons. If one assumes that it was thalamic, one also assumes that there were two separate lesions and that the third-nerve nucleus was missed. I believe that this is unlikely. The smaller pupil and the drooped lid might indicate third-nerve involvement. I consider it more likely that this was due to a lesion within the brain stem producing a mild Horner's syndrome. Conditions such as syringomyelia are apt to cause pain within the spinal cord, and perhaps a similar mechanism operated in the brain stem in this case.

#### CLINICAL DIAGNOSIS

Amyotrophic lateral sclerosis

#### DR SWANK'S DIAGNOSIS

Glioma of pons and medulla

#### ANATOMICAL DIAGNOSIS

*Metastatic adenocarcinoma, primary site undiscovered*

#### PATHOLOGICAL DISCUSSION

DR KUBIK I should like to say that this is probably one of the most difficult neurologic cases that has been presented here. Dr Swank came very close to the diagnosis when he suggested the possibility of metastases. There was an unusual type of metastasis, consisting of carcinomatous invasion of the subarachnoid space with involvement of the cranial and spinal nerves. The metastatic tumor was made up of columnar cells, which formed perfect tubules and also spread out in a single layer, covering the inner surface of the arachnoid membrane, blood vessels and cranial and spinal nerves in a most unusual and fascinating way. There was invasion of the cranial and spinal nerves and slight subpial invasion of the cord and medulla. In spite of a complete autopsy no primary tumor was found. I cannot believe, however, that a neoplasm of this type could have been primary in the central nervous system, and I assume that the primary lesion was so small that it was overlooked. We have had two or three other cases of metastatic carcinomatosis of the subarachnoid space, though none with such extensive paralyzes as this. In at least one case there were cells in the cerebrospinal fluid, and a clinical diagnosis of tuberculous meningitis had been made.

# The New England Journal of Medicine

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## OFT IN THE STILLY NIGHT —

THE public, according to complaints received by the American Medical Association, believes that it is not getting the service it requires from its doctors. A particular grievance is the difficulty — on occasions the impossibility — of obtaining emergency medical service at night.

For various reasons a reactionary attitude toward self-sacrifice has set in since the war. The devotion to a common cause in those soul-trying years elevated many persons to a heroic state of mind. Now, at least in this country, "we the people" are demanding the pay-off. We want things material, and we want them now.

The medical profession must bear its share of this failure to see eye to eye and clearly. In too many phases of its work there has been an increasing divergence from the public interest rather than an improved cordiality in public relations. The trend toward socialization has been a trend also toward the impersonalization of medical service.

During the war, 60 per cent of the nation's physicians — and they comprised the older group — remained at home, assuming their absent colleagues' duties. They were, on the whole, overworked, but, on the whole, as old-timers they accepted the responsibilities that appeared to them to be part of the obligations of a career of service. Many of them now believe that others should bear the extra burden, and this is what the others seem unwilling to undertake. The youngsters seem to have failed to acquire the idea that they have accepted a calling.

If an obligation implicit in the practice of medicine now fails of spontaneous fulfillment, however, some organized measures must be taken to provide what is lacking. The American Medical Association suggests that county medical societies or urban groups maintain telephone exchanges that will accept the responsibility for locating physicians available for emergency calls.

The majority of the older practitioners have led lives so organized that they were never, year after year, "off call" without a substitute constantly available. It is one of the responsibilities that those who care for the sick have accepted and must continue to accept: those for whom they care must never be abandoned.

## CRUSADE FOR CHILDREN

UNDER the banner of the Crusade for Children the United Nations Appeal for Children is conducting a campaign for voluntary contributions to relieve the suffering of starving children overseas. Of the national goal of \$60,000,000, Massachusetts has been assigned a quota of \$2,500,000, with \$1,500,000 to be raised in the Greater Boston area. The funds will be distributed to twenty-six religious, labor and special relief groups to supplement the inadequate amounts that governments are presently able to appropriate for relief. These agencies include the In-

ternational Children's Emergency Fund, previously separately engaged in collecting money, which has now joined them in the united appeal

The Crusade for Children is more than another campaign to persuade hard-pressed Americans to dig into their pockets for a "worthy cause." The appeal focuses attention on the plight of the children of Europe, too often overlooked in the dramatic and uncertain political situation. These children are in acute need, and quick and generous action is required to prevent the threatened disease, mental deterioration and actual death from starvation. An example of one phase of the desperate condition of European children is provided by a recent statement from the International Children's Emergency Fund which pointed out that hundreds of thousands of infants and young children are getting no milk and that others, more fortunate, are limited to less than half a pint daily.\* The Fund has been engaged in feeding nearly 4,000,000 children in twelve European countries, and extension of the aid to Germany and China is under consideration, in co-operation with the World Health Organization and the Danish Red Cross and its Scandinavian associates, the Fund is prepared to assist governments in mass-vaccination programs to check the spread of tuberculosis among the children of Europe. To these endeavors the Crusade for Children has now added the goal of saving 230,000,000 children from starvation and death.

In 1212 A.D. the children of Europe set out on the disastrous Children's Crusade to recover the Holy Sepulcher from the infidel. It is fitting that the present campaign should take the form of a crusade for children reversing the unhappy sequel to that crusade of long ago, Americans can help give enough to keep the children of Europe alive and to give them the chance of growing up healthy in mind and body. A generous contribution today may

save tomorrow's world.

\*Release from United Nations International Children's Emergency Fund dated March 2, 1948.

### "YOUR WITNESS"

A doctor's failure to give his patient at least the degree of care and skill that is ordinarily used in his community is malpractice in the eyes of the law, and civil law requires that a patient be

recompensed for the actual damage suffered from such malpractice. Whoever professes to see anything unfair about that should be thankful that he is not living in the time of Hammurabi (about [2100] B.C.), when the law required decapitation of the doctor whose patient's illness failed to respond favorably to treatment. How bitterly must the Babylonian patient of that day have regretted his doctor's very natural reluctance to undertake a cure, and with what alarm must he have viewed the increasing shortage of physicians! Forty centuries have improved conditions, but not to the point where all criticism has disappeared.

The press, the public and the legal profession point to what they consider a seriously weak spot in the doctor's reputation for unselfish public service. They say that doctors will not testify in court "against each other." They even say that it is hard to get doctors to testify "for each other." In fact, doctors do not like to go to court at all. As a result, many malpractice suits are said to be decided by juries whose only expert testimony comes from medical crackpots and disreputable hired quacks. If any or all of this is true it must be corrected.

It should at once be admitted that most doctors are reluctant to go to court, and the validity of some of their reasons should be examined. Doctors like to think of their time as more valuable than that of other people, but courts go out of their way to save a busy doctor's time. Doctors dislike the risk of being made monkeys of by belligerent attorneys, but no witness who avoids bumptiousness and confines himself to giving honest answers need fear a hostile attorney. Nobody likes the idea of testifying against his friends, but that is not what an expert witness is required to do. His obligation is to testify to the honest truth and let the jury worry about who gets hit.

And there are two sides to it. Court procedure, even now, retains some flavor of the medieval trials by battle in which plaintiff and defendant were represented by armed champions who slugged it out with more enthusiasm for winning than for establishing the truth of a claim. As expert witnesses physicians might feel easier in the kindly hands of the judge than under the practiced battle-

axes of the contending attorneys. No perfection is claimed for medicine, and there is no reason to believe that the law is perfect. Nevertheless, it would be extremely difficult to conceive of any law that would enable juries to decide medical cases fairly without the benefit of honest medical testimony and plenty of it.

This is no private matter that can be shrugged off. Doctors are news, particularly now when the right of organized medicine to manage its own affairs is being publicly questioned on economic grounds. This is no time for doctors to let the public say that it is being defrauded of its civil rights by a polite conspiracy of silence in the medical profession. Some modern Hammurabi might believe it and get the urge to dust off one of those old laws. Any thoughtful doctor would prefer to settle for an occasional morning in court.

## MOSELEY PROFESSOR OF SURGERY

DR FRANCIS D MOORE, of Boston, has been appointed Moseley Professor of Surgery at Harvard Medical School and surgeon-in-chief of the Peter Bent Brigham Hospital.

Dr Moore, who received his medical degree from Harvard Medical School in 1939, has been assistant professor of surgery at Harvard Medical School, assistant surgeon at the Massachusetts General Hospital, consulting surgeon at the Massachusetts Eye and Ear Infirmary and an associate member of the staff of the Palmer Memorial Hospital. He has become widely known for his work in gastrointestinal and thyroid surgery, as well as for his studies with the Office of Scientific Research and Development on the care and treatment of patients with burns. His investigative activities have also included the application of radioactive isotopes to surgical problems. He is a member of the editorial board of the *New England Journal of Medicine*.

The selection of such a young man (the youngest ever named surgeon-in-chief at the Peter Bent Brigham Hospital) for these posts constitutes a great honor and one that is richly deserved. As a successor to John Collins Warren, Maurice Howe Richardson, Harvey Cushing and Elliott Carr Cutler, Dr Moore will hold an enviable academic

position in American surgery, and his status at the Peter Bent Brigham Hospital is one of equal eminence. Those who are familiar with his past achievements are confident that his service will continue the great traditions of his distinguished predecessors. Both Dr Moore and the institutions concerned are to be congratulated on this choice.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

DARLING — Charles B. Darling, M.D., of Waban, died on April 19. He was in his seventy-ninth year.

Dr Darling received his degree from Harvard Medical School in 1894. He served in the United States Army Medical Corps in World War I and was a member of the original staff of the Free Hospital for Women, Brookline.

His widow, two sons and a grand-daughter survive.

McINTIRE — Herbert B. McIntire, M.D., of Cambridge, died on April 21. He was in his ninety-first year.

Dr McIntire received his degree from New York University Medical College in 1882.

His widow and a daughter survive.

ROBBINS — Albert I. Robbins, M.D., of New Haven, Connecticut, died on April 14. He was in his thirty-fourth year.

Dr Robbins received his degree from University of Vermont College of Medicine in 1939. During World War II he served with the United States Army in the Pacific area.

His widow, three sisters and four brothers survive.

## MISCELLANY

### HOSPITALIZATION OF VETERANS

The hospitalization of veterans by the Veterans Administration reached an all-time high of 109,325 on March 1, 1948. This number represents a gain of 1,874 over the previous peak of 107,451 on February 1, and an increase of 37,612 since July, 1945.

The number of veterans awaiting admission has also increased, largely owing to applications from veterans with nonservice-connected disabilities. The Veterans Administration is required to care for veterans with service-connected disabilities and may care for those with nonservice-connected disabilities if beds are available and if they affirm that they cannot afford to pay for treatment elsewhere.

## CORRESPONDENCE

### IN DEFENSE OF WHITE CROSS

To the Editor: In the February 12 issue of the *Journal*, in an article entitled "Principles of the Massachusetts Medical Society," former President Elmer S. Bagnall states:

I remember that in that same committee [Committee of Public Relations] discussion of medical-care plans later developed and that, under the brilliant and aggressive leadership of Dr. James C. McCann, the Blue Shield was conceived and launched. At about the same time the White Cross was born. This was an experiment in medical care sponsored by men who were impatient with such "inadequate" concepts for solution of problems in medical-care distribution as the Blue Shield then seemed to them. I have always thought that these men could have performed a service by reporting on the causes of failure factually and objectively.

As this is the first request from a representative of the Massachusetts Medical Society for information about the White

Cross, it seems appropriate to supply the information to correct some false impressions about the White Cross that are reflected in this quotation from Dr Bagnall's article.

First the White Cross was conceived and born in 1939 while one of the undersigned was president of the Massachusetts Medical Society. Dr McCann was appointed chairman of the committee to conceive the Blue Shield by a successor to the presidency. Thus it is obvious that the White Cross antedated the Blue Shield and was not conceived in impatience or competition with the Blue Shield.

The facts concerning termination of the White Cross may be stated briefly. Early in the winter of 1942 the officers of Medical and Surgical Associates who had assumed the responsibility of providing medical care to the subscribers of the White Cross realized that the majority of the participating family physicians and many of the consultants might enter the armed forces. Medical and Surgical Associates would then be unable to fulfill their obligations to the steadily increasing subscribers to the White Cross. Meetings were therefore held between the officers of the White Cross and Medical and Surgical Associates to meet this contingency. After a month of consultations it was decided that the possibility would actually become a fact since the majority of participating physicians were among the younger active members of the profession. It was therefore decided that Medical and Surgical Associates should avail themselves of the opportunity under the agreement with the White Cross to terminate the contract for medical service on three months' notice. When this decision was announced the subscribers asked that it be reconsidered. Several more meetings were held at which the subscribers sought means of continuing the service during the war. At these meetings the enthusiasm of the subscribers for the service was ample evidence of their satisfaction with it. The subscribers formed an independent organization and begged the Medical and Surgical Associates to continue to take care of the existing subscribers even if the rates should be considerably increased. They said they wished this because they were receiving better medical care than they had received before. With the demands of the war however no solution could be found.

We consider it fair to state that the majority of the participating physicians were interested in this experiment in the provision of complete medical care on a voluntary prepayment basis. Though they had only received approximately thirty cents on the dollar for service rendered they appreciated that more was not to be expected until the scheme had been in operation for several years. In the mean time the burden on any one physician would not be great.

Probably the most important factor in the slow though steady growth in subscribers was the opposition of many members of the medical profession to the service. Though this did not interfere with physicians' willingness to care for patients it did retard group enrollment, so essential for rapid growth and a good distribution of medical risk.

We also wish to record the interest, time and effort that the lay board of the White Cross contributed to the organization and operation of this pilot study. It is interesting that the definitions of specialist and consultant devised for this service have since been accepted and used rather widely. The concept that medical service should be built about the family practitioner supported by adequate consultant and hospital services was satisfactorily applied. In retrospect it seems however, that more organization of the consultant and hospital services is desirable in the interest of quality and economy.

This statement provides the objective thoughts desired by Dr Bagnall. The White Cross was a war casualty. To impute any other hidden cause for termination of the contract by Medical and Surgical Associates is neither objective nor factual.

For the White Cross

EDWARD A. TAYLOR, *vice president*  
HAROLD S. FULLER, *treasurer*

For the Subscribers Group

HAROLD PUTNAM, *president*  
For Medical and Surgical Associates

ALLAN M. BUTLER, M.D.  
ROBERT L. DENORMAN, M.D.  
CHANNING FROTHINGHAM, M.D.  
EDWARD L. LORING, M.D.

## BOOK REVIEWS

*Calcific Disease of the Aortic Valve*. By Howard T. Kanner, M.D., and Simon Koletsky, M.D. 8, cloth 107 pp. Philadelphia: J. B. Lippincott Company, 1947. \$5.00.

This volume, which is essentially a statistical monograph analyzes the history and pattern of a condition that has borne various names but for which the authors consider the best to be "calcific disease of the aortic valve." To the complete material derived from this review of the literature they have added the detailed study of 200 cases observed at autopsy. The book serves therefore as a valuable reference work in which both the clinical and the pathological aspects of this disease are submitted to rigorous statistical criticism.

It is pointed out that Mönckeberg first studied the condition isototically and that the most important contributions to its understanding have followed his pioneer effort, even though his emphasis on the arteriosclerotic etiology of the valvular deformity has been supplanted by growing evidence that the cause is almost always rheumatic infection.

The authors consider the factors of age, sex and race, pointing out that calcific disease of the aortic valve is largely a disease of later life, that its preponderance in males is less than has been thought (1.6:1.0) and that it is infrequent in the Negro. The heart is generally large in fact almost as large as that in syphilitic aortic insufficiency.

The pathological findings with excellent illustrations are presented in detail, as is the correlation of the aortic lesion with the stigmata of rheumatic involvement elsewhere in the heart.

The clinical examination is also carefully analyzed with consideration of angina pectoris, syncope, character of the pulse, murmurs, thrill, blood pressure and electrocardiogram. In only about half the cases in their series in which electrocardiograms were recorded was there left axis deviation. The value of visualization of the calcific aortic valve area by x-ray examination is emphasized.

Sudden and unexpected death occurred fairly often but most patients died of congestive failure.

Of 190 patients in whom a clinical diagnosis might have been made it was offered in only 48. Attention to the information and suggestions in this book should improve this diagnostic figure.

*Nutritional Disorders of the Nervous System*. By John D. Spillane, M.D. (Wales) M.R.C.P. (London). With a foreword by George Riddoch, M.D. F.R.C.P. 8, cloth, 280 pp. with 103 illustrations. Baltimore: The Williams and Wilkins Company, 1947. \$5.00.

During World War II, owing to the long confinement of prisoners of war and persons in the concentration camps there was an unusual chance to investigate nutritional disorders of the nervous system. The author studied patients with this type of disorder particularly English prisoners of war in the Far East and civilians confined in Hong Kong. In addition to his personal observations he reviewed the reports of other physicians with similar experiences in the Philippines and elsewhere. Detailed case histories are given with excellent illustrations both by photographs and by diagrams. The book contains references to the pertinent literature. This study is an outstanding one far exceeding anything of its kind previously published.

*Handbook of Psychiatry*. By Winfred Overholser, M.D., Sc.D., and Winifred V. Richmond, A.M. Ph.D. 8, cloth 252 pp. Philadelphia: J. B. Lippincott Company, 1947. \$4.00.

The authors have succeeded in setting forth modern psychiatric concepts in simple, nontechnical language. The volume has been prepared for intelligent lay persons and for relatives of mental patients, but it will probably be in the library of most specialists in psychiatry.

The material in the text, which has been presented in an undramatic, conservative manner is easily read and well organized and written with the exception of a few typographic errors. It may fail to reach the general public as the authors hoped because of its resemblance to a standard textbook of psychiatry.

Treatment of mental disorders is discussed only in a general way, self-treatment is discouraged. There is an excellent reading list at the end of each of the seventeen chapters.

The chapters on "alcohol and its role in the psychoses," "crime and mental disorder" and "psychiatric conditions in childhood," to mention only three, contain many facts and explanations that should be more generally known and understood by the public. The purpose of the authors to educate the average man and woman is indeed praiseworthy, the results may not be encouraging because the man on the street prefers picture magazines.

The clarity of the language is a tribute to the psychiatrist and the psychologist who collaborated in writing it. College students, nurses and other professional groups can read this handbook with ease and profit.

*What is Psychology? A basic survey* By Werner Wolff, Ph D. 8°, cloth, 410 pp., with 39 illustrations. New York: Grune and Stratton, 1947. \$4.00.

The author of this volume hopes to arouse a healthy skepticism of the various theories and methods in psychology and to create an interchange among collegiate classes of experiments in "depth psychology." He would have done better with an epistemologic discourse or an experimental presentation, rather than the pseudoexperimental approach taken. It appears that too much ground has been covered in too short a space to do justice to the author's points of view. The result is somewhat of a hodgepodge of experimental material and hypothetical musings, which are used sometimes to substantiate and sometimes to refute the point at issue. As a text for use with the author's own classes it may serve its purpose, its value as provocative material in other areas is questionable.

*Trichomonas Vaginalis and Trichomoniasis* By Ray E. Trussell, M.D. With an introduction by E. D. Plass, M.D. 8°, cloth, 277 pp., with 19 illustrations and 16 tables. Springfield, Illinois: Charles C. Thomas, 1947. \$6.00.

It was in 1836 that Donne discovered and named the protozoan parasite *Trichomonas vaginalis* but not until 1916 that Hoehe first described its pathogenic properties. During the past thirty years there has accumulated, on the subject of trichomoniasis and its treatment, an enormous literature that the present monograph aims to summarize and evaluate. The author has also done extensive biologic, experimental and laboratory research, and was the first to obtain the organism in pure culture. He describes in detail its history, morphology, chemical, cultural and staining characteristics, and discusses its pathogenicity and the clinical phenomena of *Trichomonas* infections. Finally he investigates its treatment and presents an alphabetical index and discussion of 185 chemical and other agents that have been utilized in efforts to eradicate it. It is noteworthy that, of the antibiotics, only tyrothricin and tyrocidin have shown any effect whatever.

The text of this authoritative work is adequately illustrated with 19 figures and 16 tables and has an exhaustive bibliography of 1586 references. One appendix summarizes the taxonomic relation of *Trichomonas* to other protozoa, and another presents a parasite-host list of 167 known species. There is an admirable introduction by Dr. E. D. Plass, professor of obstetrics and gynecology in the State University of Iowa, in whose laboratories and libraries the research was done.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Diseases of the Joints and Rheumatism* By Kenneth Stone, D.M. (Oxon), M.R.C.P., physician, B.R.C.S. Clinic for Rheumatism and Physical Treatment, Kensington. 8°, cloth, 362 pp., with 58 illustrations. New York: Grune and Stratton, 1947. \$6.50.

*Fatigue and Impairment in Man* By S. Howard Bartley, Ph.D., professor of research in the visual sciences, Dartmouth Eye Institute, Dartmouth Medical School, and Eloise Chute, M.A., research associate in the visual sciences, Dartmouth Eye Institute, Dartmouth Medical School. With a foreword by A. C. Ivy, Ph.D., M.D., vice-president, Chicago Professional Colleges, University of Illinois. First edition. 8°, cloth, 429 pp. New York: McGraw-Hill Book Company, Incorporated, 1947. \$5.50.

*Unipolar Lead Electrocardiography Including standard leads, unipolar extremity leads and multiple unipolar precordial leads* By Emanuel Goldberger, M.D., adjunct physician, Montefiore Hospital, New York City, cardiographer and associate physician, Lincoln Hospital, New York City, and clinical lecturer in medicine, Columbia University, Faculty of Medicine. 8°, cloth, 182 pp., with 88 illustrations. Philadelphia: Lea and Febiger, 1947. \$4.00.

*Radium Dosage The Manchester system* Edited by W. J. Meredith, M.Sc., F.Inst.P., Christie Hospital and Holt Radium Institute, Manchester. 8°, cloth, 124 pp., with 38 illustrations, 4 plates and 27 tables. Baltimore: Williams and Wilkins Company, 1947. \$4.50.

## NOTICES

### ANNOUNCEMENTS

Dr. Eugene Guralnick announces the opening of his office at 422 Beacon Street, Boston, for the practice of general surgery.

Drs. W. J. Mixer and C. G. Mixer announce the association of Dr. H. Thomas Ballantine, Jr., in the practice of neurological surgery at 319 Longwood Avenue, Boston.

### MASSACHUSETTS MEDICO-LEGAL SOCIETY

The annual meeting of the Massachusetts Medico-Legal Society will be held at the Hotel Statler, Boston, on Wednesday, May 26, at 2:30 p.m.

#### PROGRAM

Business Meeting

The Ruxton Case — A Study in Scientific Criminal Investigation. Robert P. Brittain, M.A., B.L., LL.B., M.B., Ch.B., Glasgow, Scotland.

Refreshments

### UNIVERSITY OF PENNSYLVANIA MEDICAL ALUMNI SOCIETY

The University of Pennsylvania Medical Alumni Society will hold a dinner at the Convention of the American Medical Association in Chicago on Wednesday, June 23, at the Lake Shore Club, 850 Lake Shore Drive. On arrival in Chicago, alumni should communicate with Miss Frances R. Houston, executive secretary of the Medical Alumni Society, at the University of Pennsylvania registration booth.

### SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 13

FRIDAY, MAY 14

\*9:00-10:00 a.m. Zioc Content of Whole Blood in Normal People and in Patients with Blood Dyscrasias. Dr. John G. Gibson, Jr., Joseph H. Pratt Diagnostic Hospital.

\*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

TUESDAY, MAY 18

\*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

\*12:15-1:15 p.m. Clinicorontogeological Conference. Peter Bent Brigham Hospital.

\*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

(Notices concluded on page xvii)

## NOTICES (Concluded from page 678)

WEDNESDAY MAY 19

- \*9:00-10:00 a.m. Human Heredity with Special Reference to Marfan's Syndrome. Dr. Isadore Ludwig, Joseph H. Pratt Doss, Boston Hospital.
- \*12:00 p.m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital.
- \*2:00-4:00 p.m. Combined Clinic by the Medical Society and Orthopedic Services. Amphitheater Children's Hospital.

\*Open to the medical profession

- May 6-8 American Association for the Study of Gout. Page xii of July 31.
- May 7 Boston University School of Medicine Alumni Association. Page 647 issue of April 29.
- May 10-18 International Congresses on Tropical Medicine and Malaria. Page 648 issue of April 29.
- May 11 Harvard Medical Society. Page 647 issue of April 29.
- May 11 New England Society of Anesthesiologists. Page 647 issue of April 29.
- May 12 South Boston Medical Society. Page 647 issue of April 29.
- May 12 Norfolk District Medical Society. Page 647 issue of April 29.
- May 12 Norfolk District Women's Auxiliary. Page 647 issue of April 29.
- May 12 and 13 Rhode Island Medical Society Annual Meeting. Providence.
- May 12-14 American Association of Genito-Urinary Surgeons. Skidmore Lodge, Skidmore, Pennsylvania.
- May 13 Indications for the Use of Forceps. Dr. Roy J. Heffernan. Perinatal Association of Physicians. 8:30 p.m. Haverhill.
- May 13 Massachusetts College of Pharmacy. Page 647 issue of April 29.
- May 13 Medical Veterans of World War II. Page 648 issue of April 29.
- May 16-22 American Board of Obstetrics and Gynecology. Page 644 issue of March 4.
- May 16-23 International College of Surgeons. Page 136 issue of January 22.
- May 17-19 American Ophthalmological Society. Page 492 issue of April 1.
- May 17-20 American Urological Association. Hotel Statler Boston.
- May 17-20 Association for the Study of Internal Secretions. Page 49 issue of April 1.
- May 17-20 American Psychiatric Association. Page 614 issue of April 22.
- May 18-22 American Association on Mental Deficiency. Copely Plaza Hotel Boston.
- May 20 Massachusetts Tuberculosis League, Inc. Page 647 issue of April 29.
- May 26 Massachusetts Medical-Legal Society. Page 678.
- June 23 University of Pennsylvania Medical Alumni Society. Page 678.

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

May 11 Annual Meeting Hotel Weldon Greenfield.

## MIDDLESEX EAST

May 12 Annual Meeting 6:45 p.m. Bear Hill Golf Club Wicked Id.

## NORFOLK

May 12 Annual Meeting Hotel Kenmore Boston.

## PLYMOUTH

May 20 Lakeville Sanatorium Lakeville.

## WORCESTER

May 12 Annual Meeting

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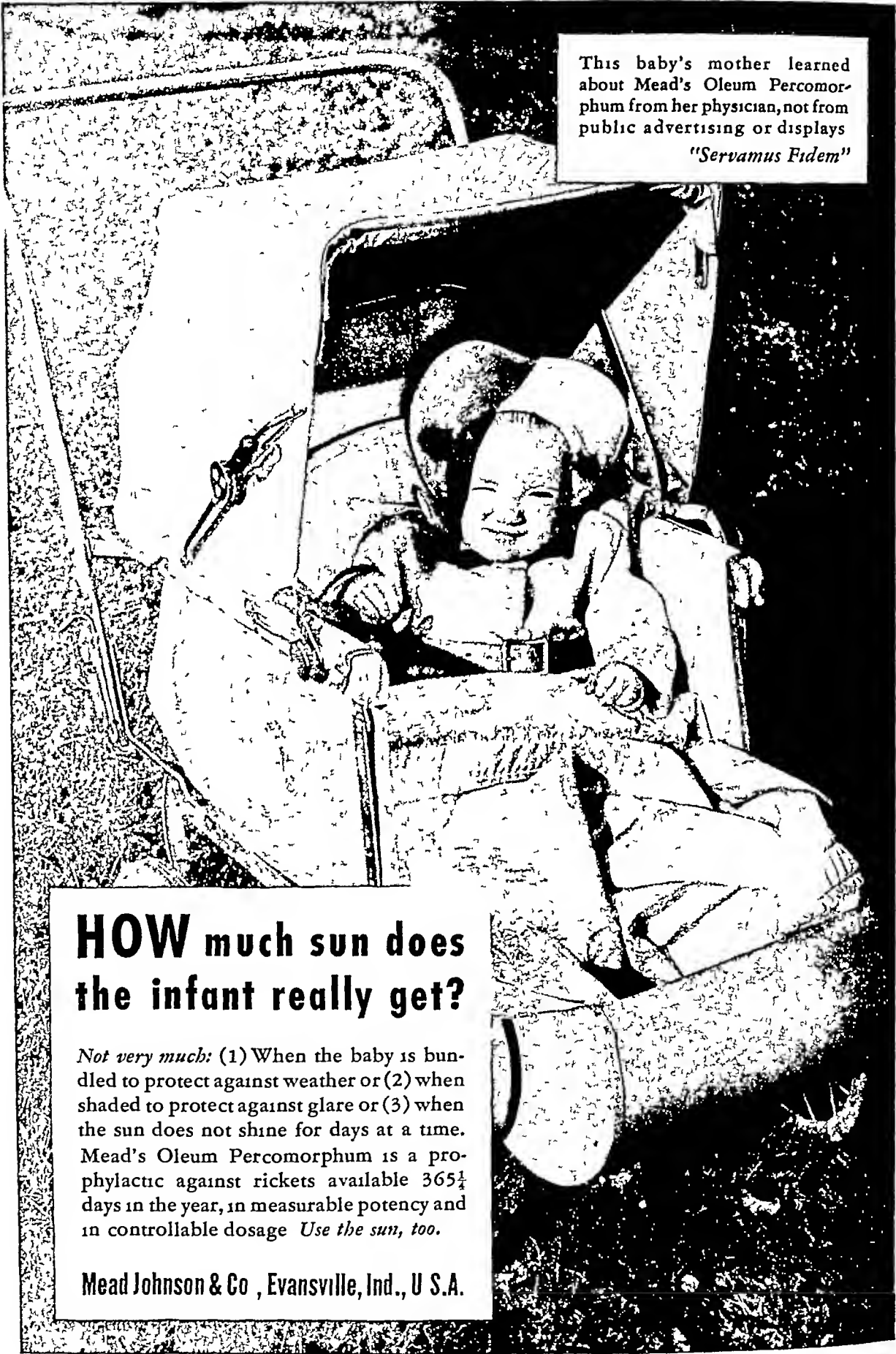
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## WHITHER THE PEGASUS OF PUBLIC HEALTH?\*

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NEW YORK CITY

TWO preoccupations require the attention of anyone responding to the call for such a lecture as the present opportunity demands. Regard for the intellectual and personal contributions of one's predecessors in this thirty-year series will create a proper humility of spirit. A hope to meet the long-ago wishes of the founder of the lecture-ship should provide the courage or perhaps explain the recklessness of one who presumes that he has a message worthy of such an academic and professional audience

\* \* \*

Whereas the original Pegasus of Greek legend seems to have been the only offspring of Neptune and the golden-haired Medusa whom Minerva so cruelly punished for the sea god's infatuation by turning her locks into serpents, ours is the winged horse on which Bellerophon rode when he slew the fabulous vanbodied Chimaera that spouted fire

The medical officer of health is modern democracy's Bellerophon, the son of Glaucus and grandson of Sisyphus, who advances upon all enemies of his fellow men on the wings of science. He is mounted on such a steed of speed and energy as will strike poetry out of the dull earth of human misery even as Pegasus of yore brought forth the fountain of the Muses, the Hippocrene on Mount Helicon, by a stamp of his hoof upon the arid rock.

Although the life history of our chosen field of scientific endeavor for society's sake is but a brief moment in the story of man, and the names of the originators of the public-health movement are few and easily recalled, I venture, instead of playing the role of thumb-nail historian, to quote two principles, or expressions of deep reasoning that seem to me to reach the essence of our problems of today and to add a sense of maturity and solidity to what has been so far a fairly successful philosophy and performance

\* \* \*

Among the papers of Abraham Lincoln revealed in July, 1947, for the first time to scholars and to students of our greatest citizen, our wisest and most beloved President, a fragment in his handwriting found in his worn carpetbag may well be remembered and taken permanently to heart by all who either share in the privilege of our suffrage or play a part as employees of civil government at any level of jurisdiction. Lincoln wrote as follows

The legitimate object of government is to do for a community of people whatever they need to have done but cannot do at all or cannot do as well for themselves in their separate and individual capacities. In all that the people can do as well for themselves the government ought not to interfere.

Perhaps we should expend less pomp and circumstance upon a mere centennial of medical organization in our country or on the seventy-five years of the American Public Health Association's life and devote more celebration to this, the six hundred and fifty-sixth year of Switzerland's independence as an autonomous representative government of a free people. The first three Cantons in 1291 entered into a perpetual pact to safeguard their system of local self-government in opposition to the officials set up by the Hapsburgs. There are threats today against the integrity and independence of our local governments by the successors in spirit of those officials

What treasures have been revealed to us by explorers into the secrets of nature had been but barren gifts if we had not held precious the principles of democratic freedom as a framework of our society within which the practical blossoming and fruiting of the sciences has been continuous and abundant. This has been obstructed only by the reminders of superstition, tradition and ignorance among us, and by the inertia and small-mindedness of a few here and there to whom the reins of government and the appropriation of tax money have been unsuitably entrusted. It is the supplementing of individual resourcefulness, initiative and responsibility by the collective authority, prestige and tax

\*The Carter Lecture on Preventive Medicine delivered at Boston November 24, 1947

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public health is necessarily set by the level of common understanding of the causes and effects, the processes and products of human physiology in terms of personal survival and social conduct. Neither virtue nor health is a necessary product of information, nor is vice a certain sequel to ignorance, but knowledge helps man escape the pitfalls of ignorance and avoid superstition and the inertia of tradition.

A valuable resource gradually being made available for small towns as well as some large cities is the health museum for visual education, a sort of temple of health, on a par of dignity, popular usefulness and aid to culture with the public library and the art museum.

Whatever is not done by the institutions devoted entirely to education to teach good sense about health from nursery classes through the university professional and graduate schools must be attempted, when of vital importance, by departments of health, if only temporarily until the needed information can be incorporated by systematic presentation in schools and colleges. The weakest phase, if not actually nonexistent for the most part, of health information through public-health agencies is that regarding the use of habit-forming drugs and self-medication with potent and hazardous sedatives, in particular the world's most recklessly used depressant, ethyl alcohol, and for the moment in this country the barbiturates. The damage to the quality of social relations, to the conduct of persons and the invariable inferiority of performance of bodily and mental functions resulting from the prevalent use of alcohol are sufficient reasons for dealing as frankly with its properties as we do with the values of cows' milk. Health officers do not dare to declare the full truth of the baleful effects of alcoholic beverages, as widely used, upon human health.

There is, besides the considerable number of opportunities for enlargement of the scope and refinement in the methods of fulfilling the existing accepted basic functions of a local health department, at least one serious defect in the present preparation of the various professional participants on its staff. We of the public-health professions lack an orderly and approved provision for field training during and after completion of the courses offered in schools of public health to physicians, sanitary engineers, public-health nurses, educators and others. State and local health departments require in-service training courses and practical field experience for each person added to their staffs. No graduate of a school of public health should be thought of as prepared for a position in a health department until he has had at least six months of supervised field training in a local health service with good standards of performance and personnel assigned to the special duty of trainee supervision.

That such training centers will be provided in the near future appears to be certain, and it may be noted here that the urgency of the need for these, and the quite unsatisfactory conditions for local rural or extra-city field training, is nowhere greater than in the New England states, and yet in these very states at present the conditions of local rural health services are not favorable for the development of such training areas.

\* \* \*

And now I am at your mercy, having ventured to glimpse the future of public health in our time, rather as I believe it should and may develop than as some of the current trends of social promotion and political opportunism would prefer it.

Frankly, I believe it would set back the hands of time, confuse public thinking, lower the respect for "state preventive medicine" and allow people to believe that more abundant care of the sick would materially improve the public health, if hospitals and other institutions for the sick were administratively included within public-health services. Regarding the following extract from a recent report on intergovernment relations in a typical agricultural county of southern Minnesota, it may be well to understand in Massachusetts also certain facts and opinions against which we must project the future administration of local public-health services.

The town meeting, city hall, and county court house are no longer the seat of local government. Alongside them and in their place have sprung up a large number of government agencies operating under a line of authority and responsibility that travels the long and circuitous route from the electorate to Washington and back to the locality. We may note that with this the cost has risen and the tax dollar is worn thin by its travels. The weakness of the existing system of public health administration is not due to lack of organization of any single unit or agency in the field of public health, but rather, to the disconnected operation of many agencies engaged in similar activities.

State and federal funds have been slow in making their way into the community. Nearly all federal grants and state appropriations are used directly to finance the activities of state administrative agencies, a very small part is passed on to local units to support programs of their own.

In Blue Earth County of Minnesota with about 40,000 population a careful study revealed 155 units of local government charged with many similar and oft-times over-lapping functions, some 105 state agencies and 38 federal agencies with offices in the county, a total of 298 units and agencies of government serving the people of this county, exclusive of the over-all ministrations of the state and federal governments.

Of our 155,000 units of government in the United States, we have about 150,000 too many.

Admitting that we have too many governmental units—one for every 850 people and every 19 square miles—it is highly improbable that we shall see any marked decrease through compulsory methods for many years to come. It is more likely that a desirable reduction in the number of governmental units will come only after practical demonstration of cooperative action along functional lines.

Let me close by briefly putting before you the structure of public health as I see it, a possible and

certainly desirable function of civil government. First in time and importance will be the 1200 or so units of local health administration (instead of the present 18,000 health departments), from the least of perhaps no more than 30,000 persons, and preferably not less than 50,000, to the largest and one of the oldest, the five-county unit of the City of New York.

These will be the chief instrument of public health in the United States, with the consultative, advisory, standardizing and probably financial backing of the state departments of health and the long-awaited single federal health authority, the last also giving invaluable support through financial and technical aid and the benefit of its interstate and national functions. Federal aid will be based on evidence of a competent state plan for total coverage by local services whose functions, methods and personnel have been officially declared, and then funds will be available only to units recognized as too economically disadvantaged to meet the cost of their health department from local and state tax resources alone.

With such a nation-wide administrative structure the basic functions will first be performed with increasing approach to competence before the diversion of dollars and personnel to other and less productive even though temporarily popular activities take place. We have the authority, the technical knowledge, the practical "know-how" to justify a future of higher goals, to make an en-

during success of the trial marriage of medicine, or the art of human biology, and representative civil government on our familiar pattern of a democracy. We need better methods, more critical self-analysis, the use of administrative epidemiology, as well as better trained personnel and more liberal conditions of their employment.

\* \* \*

For all, the health benefits now available to part of our people shall follow. And when it is all said and done we find in the few lines from Shakespeare that it need not have taken so many words of mine to relate or so many of your precious collective minutes to listen.

"If to do were as easy as to know what were well to do, chapels had been churches and poor men's cottages prince's palaces."

And without more to-do let us mount our Pegasus of today, and as the Bellerophons of modern democracy lead our fellow men, women, and children to heights of health that can be seen at a distance, but not out of reach for those who accept the hazards of leadership.

Let us who are concerned professionally with the career of public health concentrate the resources of the sciences and of civil government upon the prevention of disease, relying upon the age-old guild of practitioners of the healing art to provide the skills and humane consideration due the sick and suffering.

600 West 158th Street

## RECONSTRUCTION OF THE BURNED HAND\*

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HANOVER, NEW HAMPSHIRE

**R**ECONSTRUCTION of the burned hand starts at the time of the initial dressing. Intelligent treatment during the first month will effectively prepare the hand for later restorative procedures, whereas misguided handling may thwart all efforts to bring back full function.

### EARLY TREATMENT

It is generally agreed that the immediate local treatment of a burned hand includes a minimal amount of debridement confined at most to the gentle removal of vesiculated epidermis and the application of a firm, even pressure dressing. The fingers should be packed individually, and the entire hand encased in a bulky, fluffed-gauze dressing retained by a snug elastic bandage. The position of the hand within the pack is important. Fingers

should be spread, and all joints fixed in moderate flexion, a position easily obtained by having the hand grasp a large gauze ball. This also brings the thumb well away from the index finger into a position of opposition. The wrist is supported by a light dorsal plaster splint in slight dorsiflexion. In other words, the hand is immobilized in a position of function where any permanent limitation of motion will prove least deleterious.

Cope and his associates<sup>1</sup> have called attention to the manifest advantages of the immediate or early excision of severely burned areas and replacement by free skin grafts. Although this method has a place in the treatment of the burned hand, one must appreciate the fact that the anatomic features of the hand, with its dearth of subcutaneous tissue, necessitate a dissection uncomfortably close to important structures such as the extensor tendons and the aponeuroses of the fingers. Unless a graft can be applied accurately and made to adhere com-

\*Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 3, 1947.

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pletely, the result may be damaging to function, hence the method should probably be reserved for

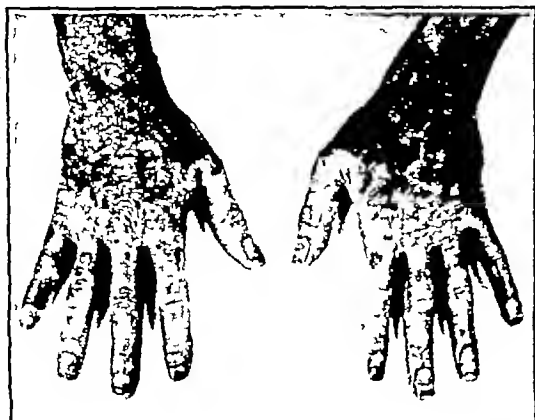


FIGURE 1 Photograph Showing Spotty Depigmentation of the Skin after a Severe Burn

cases of localized burn in which the possibility of any significant loss of graft is slight

If a paste of pyruvic acid and starch<sup>2</sup> is used to hasten the extrusion of slough, one can still retain the position of function when dressings are applied

First consideration should be given to mobilizing the hand as early as possible to minimize edema and to maintain joint action. Therefore, active and passive exercises should be started even before the grafts are fully stabilized, the attendant watching carefully for bleb formation and splinting any such area until the tendency to loosen has passed. New grafts and newly formed skin must be carefully protected. The patient can do this consciously during the waking hours, but at night protective dressings should be reapplied to guard against trauma during sleep. This is the best time to correct incipient contractures. Proper positioning of the digits on a night splint, with gentle elastic traction at strategic points, should maintain a functional position throughout this phase of stabilization of integument. Once this state is reached one can start a program of occupational therapy and await softening of scar and improved nutrition of the hand before considering a more permanent type of replacement. In many cases the primary graft may prove quite satisfactory, and no further resurfacing will be needed.

#### LATER RECONSTRUCTION

Skin presents a curious variation of response to thermal injury. One type occasionally seen is the



FIGURE 2 Preoperative (A) and Postoperative (B) Photographs of Contracting Scar Replaced by a Near-Full-Thickness Graft from the Abdomen  
Note the broken line crossing the dorsum of the wrist

This likewise applies to the phase of moist dressings that may be used to prepare the wound for grafting

Any granulating areas should be resurfaced as soon as the nutrition of the wound permits. Exuberant granulations are shaved down and covered with split-thickness skin grafts of 0012 to 0018 inches. It is desirable to excise intervening areas of spotty epithelium, but attempts to carry out a complete resurfacing of the dorsum of the hand and fingers, including a dissection down to the investing membranes of the tendons, had best be deferred to a later time.<sup>3</sup>

spotty depigmentation of the dorsum (Fig 1), which is not necessarily associated with keloid or contracture, but which in itself may offer sufficient reason for replacement. One should be sure that the process has become stationary, however, since pigmentation often returns in the course of time.

Hypertrophic keloid is a common manifestation of burned skin. It is desirable to wait until the erythematous phase has subsided before proceeding with replacement unless contractures demand early attention. In equivocal cases it is well to temporize

since even heavily developed keloids will soften within the course of months

The principal indication for resurfacing is the presence of constricting or unstable scar. A hand

the abdominal wall. Hence for expediency the split-thickness skin graft,<sup>4</sup> taken either free hand or with a dermatome, is usually employed. This gives adequate stability, does not contract unduly



FIGURE 3 Photographs Showing Constricting Keloidal Scars of the Dorsum of the Hands (A) and Replacement by Split Thickness Grafts (B)

Note position of line of juncture of grafts at base of right thumb (C)

enclosed in the vise-like grip of a burn scar is lacking proper nourishment as well as suffering from the mechanical effects of the tightness. A scar that tends to form superficial ulcerations at the slightest trauma is a severe economic handicap.

A most satisfactory type of resurfacing employs the near-full-thickness skin graft, which is dissected

and in most cases furnishes an inconspicuous color tone.

At the Hitchcock Clinic dorsal resurfacing procedures are carried out under a tourniquet. The scar is elevated at its natural cleavage plane, and the dissection carried to the line dividing volar and dorsal surfaces of the hand and of any affected



FIGURE 4 Photographs Showing Severe Contractures and Imbedding of the Volar Aspects of All the Fingers of the Right Hand in Scar (A) and Release of Contractures by Free Grafts of the Entire Volar Surface and Part of the Dorsum (B)

The useless little finger has been amputated

off the abdominal wall by scalpel and the defect closed by undermining after the remaining thin sheet of dermis has been removed (Fig 2A and B). Although this gives excellent stability with a minimum of shrinkage, the method requires both a great deal of time and an extensive procedure on

digits. Only the portions of the digits that show tightness or instability are denuded. The tourniquet is then released, and hemostasis effected.

Split-thickness skin grafts approximately 0.022 inch thick are removed with a dermatome. For complete coverage of the dorsum of a hand one

and a half drums are removed. The graft comprising one full drum is used to cover the fingers and their metacarpals. The half-sized graft will cover the thumb and the triangle at its base. All suture lines are placed so as to avoid contractures

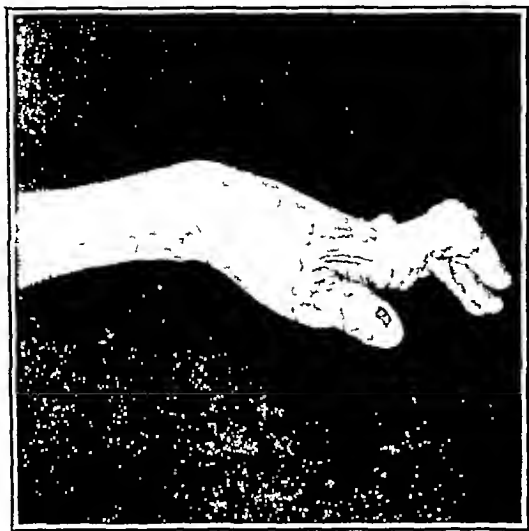


FIGURE 5 *Complex Contractures of the Fingers Involving the Joint Capsules*  
*Replacement of scar by free grafts has not overcome the deformity*

(Fig 3) Lines extending across expanding and contracting portions of joints are avoided if possible. When such a line is necessary it is broken into oblique components by means of a dart (Fig 2B). The grafts are trimmed to fit the defect accurately

guard against excessively tight bandaging, which has been known to cause ischemic contracture.

In cases of more extensive damage, particularly in cases in which digits are involved, the base may be unsuitable for free grafting, or the loss of tendons and joint capsules may necessitate further reconstructive work. Such cases necessitate the more protracted method of resurfacing by means of direct pedicle flaps using skin and underlying fat from the abdominal wall or from the opposite arm.

Burns of the volar surface of the hand, although less frequent, are usually associated with severe damage to the hand generally and present baffling problems in restoration. If flexor tendon sheaths are preserved one may find it possible to release contractures by free grafts (Fig 4), otherwise it may be necessary to use a tubed pedicle flap through which corrective procedures on the tendons and joints may be carried out later.

Contractures of the interdigital webs are an almost constant finding in significant burns of the dorsum of the hand. When a free graft is applied dorsally this web may be broken by carrying a point of the graft well down to the volar aspect.

Residual joint contractures may be produced in various ways. Lack of splinting will allow severely burned hands to assume grotesque positions. On the other hand improper splinting, particularly immobilization on a flat splint, may result in complex contractures of the digits and adduction contracture of the thumb.

A common type is extension contracture of the metacarpophalangeal joints due to tightening of skin

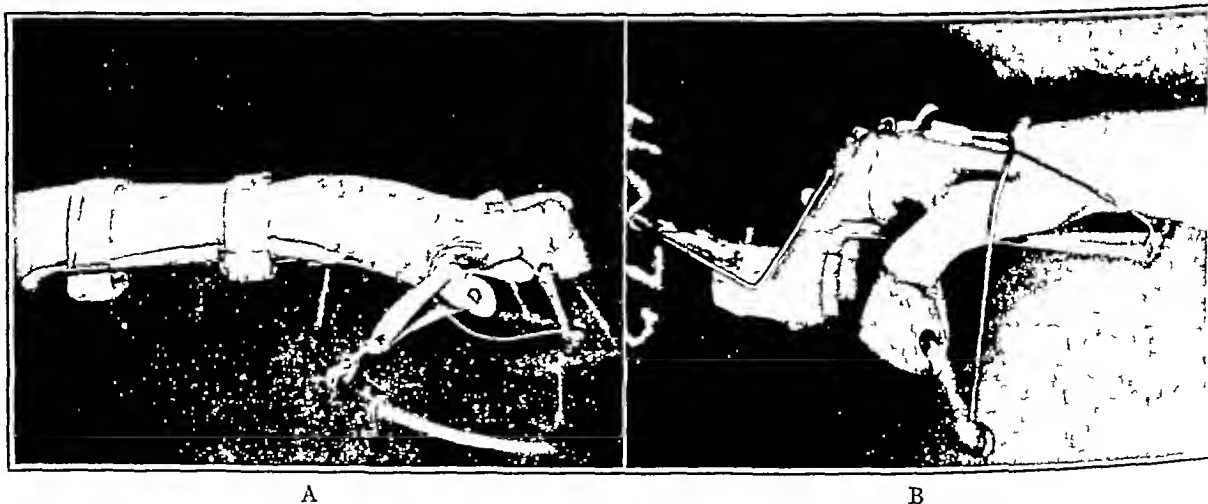


FIGURE 6 *Two Types of Splint (A and B) Used to Produce Flexion of the Metacarpophalangeal Joints, Extension of the Proximal Phalangeal Joints and Abduction and Opposition of the Thumb*

and are sutured to the wound margins without overlapping. Firm, even pressure is applied by careful packing, and the hand immobilized in a functional position as described above. Although the dressing should be applied snugly, one should

and shortening of extensor tendons. The almost invariable concomitant of this contracture is a flexion contracture of the proximal phalangeal joints (Fig 5). If skin replacement fails to correct this deformity one should use a splint of the type repre-

presented in Figure 6A and B, which, while permitting active exercise, maintains elastic traction to straighten the finger contractures and to bring the thumb away from the index finger and into opposition.<sup>8</sup> If corrective splinting fails capsulectomy may improve position of the metacarpophalangeal joints and if this is ineffective, fusion is indicated. Occasionally it has proved advantageous to perform a capsulectomy of the metacarpophalangeal joints at

splinting of the thumb in a position of function, but if integumentary loss has been significant a free graft will be needed to permit adequate abduction. If the contracture has been existent for a long period, simple replacement of skin will not correct the deformity inasmuch as the adductor muscles will have become shortened and fibrotic. This condition can be improved if one detaches the adductors from their insertions at the base of the

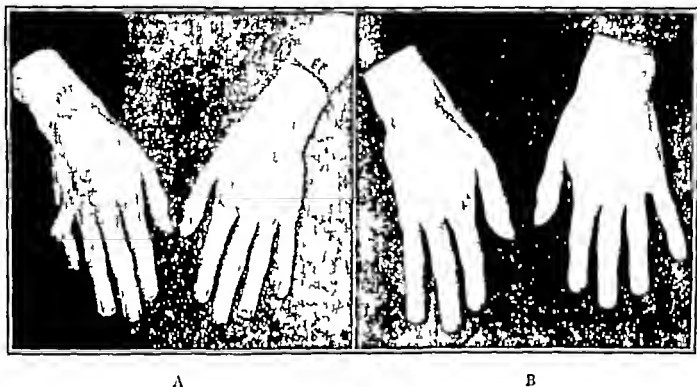


FIGURE 7 Photographs Showing Keloidal Scarring of the Dorsums of Both Hands with Complex Contracture of the Right Little Finger (A) and Correction by Amputation of the Little Finger and Part of its Metacarpal (B) Skin of the Amputated Finger Being Used to Release Extension Contracture of the Ring Finger

The dorsum of the left hand has been resurfaced by a free graft.

the time of resurfacing, as described by Shaw and Payne,<sup>8</sup> which permits proper positioning of the fingers when the grafts are applied.

The little finger is particularly prone to develop complex contracture. If the deformity is severe I have occasionally amputated the finger, together with part of the fifth metacarpal bone, thereby giving the patient a stable, well functioning hand of reasonably satisfactory appearance and avoiding a long program of reconstruction that at best offers only partial function (Fig 7).

Another frequently noted deformity is a flexion contracture of the metacarpophalangeal joints. This often signifies that the extensor tendon and the hood have been destroyed or split, allowing the two halves to slide off the prominence of the knuckle into the intermetacarpal fossae. The initial correction should consist of an extension splint to the proximal phalanges to overcome the unopposed action of the long and intrinsic flexors, and then of replacement or resurfacing of the damaged extensor tendon and hood mechanism.

Flattening of the thumb with adduction contracture may be minimized by early and effective

first phalanx and reattaches them more proximally on the first metacarpal, deepening the web and permitting the thumb to fall into a more abducted position.

#### SUMMARY

Restoration of a burned hand starts with initial immobilization in a functional position.

Early replacement of constricting or unstable scars is most important in restoring proper nutrition and avoiding contractures.

Proper elastic splinting should be employed not only in the correction of contractures but also, more assiduously, in the prevention of contractures.

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# PHEOCHROMOCYTOMAS COEXISTING IN ADRENAL GLAND AND RETROPERITONEAL SPACE, WITH SUSTAINED HYPERTENSION\*

## Report of a Case with Surgical Cure

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**P**HEOCHROMOCYTOMA as a cause of hypertension is being more frequently recognized than it was a decade ago. There are several reasons for this.

In recent years physicians have become increasingly familiar with the variegated symptom-complex produced by these tumors.

The recent trend for complete diagnostic survey in patients with high blood pressure leads occasionally to the discovery of an unsuspected adrenal tumor.

Emphasis on the part of many observers that these tumors may produce persistent unremitting hypertension clinically indistinguishable from essential hypertension has led to a greater suspicion of their presence in the study of hypertensive patients.

Improved technics in the diagnosis of early enlargements of the adrenal gland, such as intravenous pyelography and perirenal insufflation of air and other gases, have helped immeasurably in the localization of tumors too small to be demonstrated by other nonsurgical means.

Thoracolumbar sympathectomy, which brings the adrenal gland into view on the operating table, is being done with increasing frequency for the treatment of hypertensive disease.

Complete cure of the syndrome, with return of the blood pressure to normal, is not an infrequent sequel to surgical extirpation of the tumor. The operative mortality in these cases has recently been strikingly reduced as a result of increasing knowledge regarding epinephrine shock and its control by appropriate administration of adrenalin and the adrenal cortical extracts when indicated.

Multiple pheochromocytomas occur rarely. Of the surgically cured cases of pheochromocytoma recently summarized by MacKeith,<sup>1</sup> all were solitary. The following case report is thought to be of interest because it represents the first recorded case of multiple pheochromocytomas surgically cured.

## CASE REPORT

A 12-year-old girl of Italian extraction was admitted to the hospital in September, 1943, because of excessive perspiration and increased appetite with failure to gain weight. The illness had begun 2 years before admission, when she first noticed a tendency to sweat profusely. She began to be intolerant of heat. Her appetite became excessive, and yet she had gained no weight, and shortly before admission she had begun to lose weight. She noticed excessive thirst and drank large quantities of water. She complained of easy fatigability and of palpitations, stating that the heart often beat fast, even without exercise. Occasionally, she sensed numbness and tingling in the hands. Two determinations of the basal metabolic rate before admission had been reported as +50 per cent and +30 per cent.

The past and family histories were noncontributory. Physical examination disclosed an undernourished, apprehensive, emotionally unstable girl. The skeletal development was good. The skin was always warm and moist. The eyes showed no evidence of exophthalmos, and the eye grounds were normal. The eye signs of thyrotoxicosis were conspicuously absent. The thyroid gland was not palpably enlarged. The chest was clear. The heart was not enlarged, and the rhythm was regular. No murmurs could be heard. The liver edge was felt two fingerbreadths below the right costal margin. No abdominal masses could be felt. Application of pressure over the abdomen failed to influence the level of the blood pressure. The reflexes were physiologic.

The pulse consistently averaged 120, and the blood pressure 180/120, the hypertension being unremitting and not paroxysmal.

Examination of the blood revealed a normal red-cell count, hemoglobin, white-cell count and differential count. Urinalysis showed a specific gravity of 1.024, a slight trace of albumin, no glucose and an occasional white cell in the sediment. The glucose tolerance test gave a diabetic type of curve. The fasting blood sugar was 88 mg., and the non-protein nitrogen 34.6 mg. per 100 cc. The blood iodine level was 4.8 microgm. per 100 cc. (normal average 6.2 microgm.). Several determinations of the basal metabolic rate varied from +51 to +67.6 per cent. The serum cholesterol was 215 mg. per 100 cc. An electrocardiogram showed sinus tachycardia. X-ray films of the skull and the chest were normal. A plain film of the abdomen disclosed a tiny area of calcific density in the region of the left suprarenal shadow.

The patient was observed repeatedly for the next 9 months, during which the physical findings remained unchanged except that by June, 1944, the blood pressure had risen to 200/150 and a soft, blowing systolic murmur could be heard over the apex. The eye grounds showed blurring of the disk margins, with papilledema. The arteries were markedly narrowed, and the veins showed nicking at the arteriovenous crossings. Several fluffy-white exudates and a flame-shaped hemorrhage could be seen. These signs of hypertensive retinopathy progressed rapidly while the patient was under observation.

A trial with Lugol's solution failed to influence the clinical state.

Intravenous pyelograms were normal. Bilateral perirenal insufflation of air was carried out, and considerable enlargement of the left adrenal gland was visualized on the x-ray film (Fig. 1).

A diagnosis of tumor of the left adrenal gland, probably intramedullary pheochromocytoma, was made, and through an extraperitoneal lumbar approach, the left adrenal gland was explored and found to contain, in its midportion, an encap-

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enlarged globular tumor 2.5 cm in diameter. The blood vessels leading to it were found to be dilated. Manipulation of the tumor while the patient was under anesthesia caused a rise in the blood pressure from 170/120 to 200/160 and in the pulse from 130 to 170 but with removal of the tumor the blood pressure fell to 60/30, requiring intravenous adrenalin intramuscular adrenalin-in-oil and 10 cc. of adrenal cortical extract (eschatin) subcutaneously. It was thought that a mass distinct from the adrenal gland could be felt but in view of the patient's condition, further exploration and further surgical exposure seemed unduly hazardous and were not carried out.

The tumor weighed 6 gm. It was yellow, soft and lobulated containing two small, triangular shaped, red areas suggestive of infarction. Microscopically it was composed of rounded masses of cells, with large nuclei containing fine distinct granules and fine threads of chromatin which could be seen as greenish brown granules in the cytoplasm when stained with Schmorl's stain (Fig. 2). The capsule consisted of a thick fibrous layer. The tumor showed no inclination to pass this barrier and was considered a cytologically benign pheochromocytoma. Treatment with ferric chloride solution yielded a deep olive-green color indicating the presence of adrenalin or an adrenalin like substance in the tumor. A qualitative test of the tumor was made for adrenalin by Dr. C. Harrison Snyder, Jr. An acid aqueous extract

still present. This impression was given support by the suspicion of a mass that, at the time of the first operation, had been thought to be present and also by the benzodioxane studies.

Eight weeks after the first operation, the abdomen was explored, and in the left retroperitoneal space, a spherical tumor, 4 cm in diameter, could be felt and was found lying medial and cephalad to the left adrenal gland and quite distinct from it. This was removed through a left subcostal

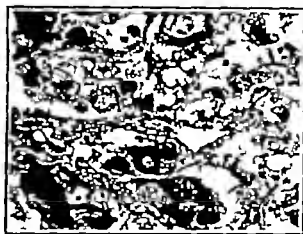


FIGURE 2. Photomicrograph Showing the Histopathology of the Benign Intramedullary Pheochromocytoma

Note the presence of large, irregular cells with deep-staining granular cytoplasm and eccentric nuclei. The granules appear greenish in Schmorl's stain.



FIGURE 1. Plain Film of the Adrenal Glands Taken after Bilateral Perinephric Air Insufflation.

Marked triangular enlargement of the left adrenal gland due to the presence of the intramedullary pheochromocytoma is seen. The right adrenal gland is not enlarged. Note that the position and axis of the left kidney are not remarkable.

of the tumor was prepared and a few drops placed in the conjunctival sac of a rabbit upon which a unilateral cervical sympathectomy had previously been done. The eye on the normal side was not affected but the denervated eye dilated maximally even with high dilutions of the extract. This test, although not quantitative is considered highly specific for adrenalin.

After the removal of the intra adrenal pheochromocytoma the blood pressure fell to a level lower than that before operation, and symptomatically the patient experienced relief from the excessive sweating. However the blood pressure was still pathologically high averaging 160/144. It was considered likely that there was some adrenalin-producing tissue

oblique transperitoneal incision. It probably originated in the first or second lumbar sympathetic ganglion.

The tumor was encapsulated rubbery in consistence and yellow green. It had essentially the same architectural pattern as the original intra-adrenal tumor. Schmorl's stain again showed large amounts of chromaffin material.

Postoperatively the blood pressure fell to 138/100. Six months after operation the blood pressure had fallen to 114/54. The patient was completely asymptomatic. The excessive perspiration and ravenous appetite had disappeared. She had acquired a healthy respect for the cold and no longer experienced any palpitation or numbness and tingling in the extremities.

One and a half years after the second operation she was in vigorous health having gained 28 pounds in weight. The blood pressure was 116/78, the basal metabolic rate was +5 per cent, visual acuity was 20/20 and there was complete disappearance of papilledema, hemorrhages and exudates. She was apparently completely normal.

#### CLINICAL ASPECTS

Many adequate descriptions of the syndrome of paroxysmal hypertension due to tumors of the adrenal medulla have been given in the literature and need not be reviewed. Although the disease is thought to present symptoms of paroxysmal attacks of hypertension, with copious perspiration, tachycardia, palpitation, headache, numbness and tingling in the extremities, there has been a tendency on the part of recent authors to emphasize the statement that the hypertension may be well sustained and need not be paroxysmal. In this way, the distinction between this disease and malignant hypertension may present real diagnostic difficulties, as pointed out by Palmer and Castleman.<sup>1</sup> In other words, the discharge of adrenalin or some adrenalin-like pressor substance from the tumor need not be paroxysmal, but may be continuous. Indeed,

Howard and Barker<sup>3</sup> concluded from their study of 18 cases that persistent hypertension is too common in this disease to be ignored as part of the syndrome. Quinby<sup>4</sup> has also reported persistent hypertension in pheochromocytoma.

The hypermetabolism noted in the case presented above has been previously described. McCullagh and Engel,<sup>5</sup> of Cleveland, reported 2 cases with high basal metabolic rates. The differential diagnosis between pheochromocytoma and hyperthyroidism was facilitated in the case reported above by a normal blood iodine level. The poor response to Lugol's solution was also considered strong evidence against hyperthyroidism.

The differential diagnosis between psychoneurosis and hysteria on the one hand and pheochromocytoma on the other may present some difficulties, as pointed out by Van Epps et al.<sup>6</sup> Peculiar sensations, such as choking and a full feeling in the neck, precordial and substernal distress, are symptoms difficult to evaluate. The numbness and tingling of the extremities, with blanching on one occasion, suggested the possibility of an angiospastic condition such as Raynaud's disease.

A remarkable case of hypertension associated with diabetes was reported by Duncan, Semans and Howard.<sup>7</sup> After removal of the pheochromocytoma the blood pressure fell to normal, and the diabetes mellitus completely disappeared.

It is significant that intravenous pyelograms failed to disclose the presence of a suprarenal tumor. In 11 of the 18 cases studied by Howard and Barker,<sup>3</sup> the adrenal tumors were diagnosed by pyelography. If perirenal insufflation of air had not been resorted to, the intra-adrenal tumor in the case reported above would have been missed, since pyelographic demonstration of displacement of the kidney and alteration in its axis was insufficient to suggest the presence of a tumor in the left suprarenal space. Cahill<sup>8-10</sup> has stressed the importance of perirenal air insufflation in the localization of small enlargements of the adrenal gland that can be preoperatively identified in no other way.

Other laboratory determinations have been found to show some departure from normal. The serum potassium has been found elevated, as has the urea clearance. The explanation given by McCullagh and Engel<sup>5</sup> for the increased urea clearance is the "rapid flow of blood through the tissues." The administration of adrenalin to a normal subject produces a decrease in renal blood flow, an unchanged rate of glomerular filtration and a marked increase in filtration fraction—changes indicative of afferent glomerular arteriolar constriction.

The peripheral blood flow is decreased during hyperadrenalinemia. The skin temperature is reduced, and the peripheral resistance is increased. In a patient with pheochromocytoma Evans and Stewart<sup>11</sup> observed these changes, which were reversed after removal of the tumor. These authors

explain the attacks of perspiration as resulting not from direct autonomic sympathetic stimulation of the sweat glands but as a response of the body to a state of increased heat production (as produced by the hypermetabolism and noted in the elevated temperature) combined with decreased peripheral blood flow. Profuse perspiration leads to cooling by evaporation, the excess heat being thus dissipated.

By 1940 only 11 cases of extra-adrenal pheochromocytoma had been reported, 9 of these were tumors of Zuckerkandl's organ, 1 was in a retroperitoneal ganglion near the origin of the superior mesenteric artery, and 1 was intrathoracic, occurring in the right pleural cavity paravertebrally at the level of the sixth intercostal space. In 1940 Phillips<sup>12</sup> reported a second intrathoracic pheochromocytoma that clinically masqueraded as a tumor of the left apical sulcus at the level of the first intercostal space with Horner's syndrome. The patient died of cardiac decompensation and a stroke. Autopsy showed normal adrenal glands, advanced renal arteriosclerosis and a pheochromocytoma in the region of the apex of the left hemithorax.

Thus, the clinical aspects of this disease are variable and may suggest such unrelated pathologic processes as tumor of the superior sulcus, Raynaud's disease, essential hypertension and psychoneurosis.

#### PATHOLOGY

Pathologically, the tumor arises from the pheochromoblast cell. This is to be distinguished from the sympathoblast cell, which represents the anlage of the sympathicoblastomas, or neuroblastomas, a tumor unrelated to the syndrome under discussion. Goldzieher<sup>13</sup> has outlined the genetic development of tumors of the adrenal medulla. These are derived from the parent cell, or sympathogonia, which in the course of embryologic development, differentiates into the sympathoblast and the pheochromoblast. The sympathoblast gives rise to the ganglion cell whereas the pheochromoblast gives rise to the pheochromocyte, from which cell type are derived the cells of the chromaffin system, first described by Kohn,<sup>14</sup> in 1903, as consisting of chromaffin or chromophilic cells found along the entire length of the autonomic nervous system occurring in the autonomic ganglions as nests known as chromaffin bodies or paragangliomas. In addition, the chromaffin system includes the adrenal medulla, carotid body and Zuckerkandl's organ, which comprises two small chromaffin bodies lying anterior to the aorta near the inferior mesenteric artery.

It should be pointed out that although any chromaffin body may at least theoretically develop a tumor called a chromaffinoma or pheochromocytoma, such a tumor need not produce the hypertensive syndrome. Cragg<sup>15</sup> has shown that there is no necessary correlation between chromaffinity and

the presence of epinephrine. Thus, by 1943, 275 cases of carotid-body tumors had been reported, and in none of these was hypertension present. It appears that chromaffinomas of the carotid body do not produce hyperadrenalinemia. Tumors of Zuckerkandl's organ, on the other hand, may or may not produce adrenalin.

The tumors that produce hypertension are usually found to contain increased amounts of adrenalin when analyzed. Normally, the adrenal glands contain 0.4 mg per gram of tissue, but some tumors have been found to contain as much as 20 mg per gram.

The chromaffinoma stains yellow with Zenker's chromate solution, and this chromate fixation is characteristic of the tumor. Cytologically, these tumors consist of polyhedral cells arranged in nests or masses, containing abundant cytoplasm, but varying considerably in size and shape. They often show hemorrhagic cysts.

The tumors may be unilateral or bilateral, benign or malignant. MacKeith<sup>1</sup> showed that 97 per cent were bilateral and 9 per cent were malignant. Thus, in most cases of this syndrome, one may reasonably expect to find a single benign tumor as responsible pathologically for the symptom complex.

There has been an interesting association of cutaneous neurofibromatosis with pheochromocytoma in 9 of the 165 cases of adrenal tumors reported by MacKeith.<sup>1</sup> Most of these have been in bilateral adrenal tumors.

Autopsy studies reported by Howard and Barker<sup>2</sup> revealed that nephrosclerosis was an uncommon finding and that when it was present, it was of mild degree.

#### 1164F (DIMETHYL PIPERIDINOAMINOMETHYL BENZODIOXANE)

Pharmacologic interest in dioxane drugs dates back to 1933, when Fournneau<sup>16</sup> reported synthesis of some of these derivatives. One of these, 933F (piperidino-methyl-benzodioxane), has been studied extensively. In 1934 deVleeschhouwer<sup>17</sup> showed that 933F reverses the hypertension produced by adrenalin in the chloralosanized dog and reduces or abolishes the smooth-muscle response to adrenalin, leaving unimpeded the nerve stimuli.

Katz and Friedberg,<sup>18</sup> in 1939, produced in trained, unanesthetized dogs, a reversal or inhibition of the adrenalin pressor action with 933F in doses of 1 to 5 mg per kilogram of body weight.

Monson and Lissak<sup>19</sup> showed that 933F accelerates the inactivation of adrenalin in vitro.

The theory of Rosenblueth and Cannon<sup>20</sup> regarding the mechanism of this antiadrenalin action of 933F suggests that this dioxane derivative increases the polarization and decreases the permeability of smooth muscle, blocking the passage of adrenalin to its site of action inside the smooth-muscle cell—that is, 933F polarizes the effector cells and thus limits the penetration of circulating chemicals (such

as adrenalin) without affecting the activity of mediators liberated intracellularly by the nerves.

The possible use of benzodioxane derivatives as indicators of hyperadrenalinemia in clinical diagnosis was first suggested by Biskind, Meyer and Beadner<sup>21</sup> in 1941. Previously, the demonstration of hyperadrenalinemia depended upon the modified Pissemaki method of perfusion of a rabbit's ear with blood drawn from a patient having an hyperadrenalinemic crisis—as done by Beer, King and Prinzmetal<sup>22</sup> (1937), who demonstrated a reversal effect with ergotamine. This is a cumbersome test requiring special technical facilities that are not easily available in many laboratories.

The effect of these drugs on experimentally produced hypertension in animals has been studied by Bing and Thomas<sup>23</sup> and by Goldblatt,<sup>24</sup> and it has been shown that renal hypertension is not significantly influenced by the intravenous administration of one of these derivatives, 883F (di-ethyl amino methyl benzodioxane).

Sapirstein and Reed,<sup>25</sup> using 933F intraperitoneally, produced no change in the blood pressure of normal rats and in the blood pressure of rats made hypertensive by the partial ligation of one renal artery.

Recent studies by a group at the Columbia-Presbyterian Medical Center—comprising Dr Henry Aranow, Jr, and Dr Marcel Goldenberg, of the Medical Service, and Dr C. Harrison Snyder, Jr, of the Babies Hospital—suggest that the blood-pressure level in patients with essential hypertension is not significantly influenced by the intravenous injection of 1164F (dimethyl piperidinoaminomethyl benzodioxane), another representative dioxane derivative. These workers thought it reasonable to expect that the blood pressure in patients with hyperadrenalinemia would show a demonstrable fall if one of these drugs were injected intravenously.

When, after the removal of the intra-adrenal tumor, a solution of 1164F was injected intravenously in the case presented above, a significant drop in blood pressure from 160 systolic, 144 diastolic, to a normal level (100 systolic, 60 diastolic) ensued. Upon cessation of the injection, the blood pressure rose to its preinjection level, only to fall to normal again upon repeated intravenous injection of 1164F. The dose of each injection was 15 mg of the dry powder dissolved in 1.5 cc of sterile distilled water given intravenously in a two-minute period during a continuous intravenous drip of physiologic saline solution.

The results of this test suggested the possibility of residual hyperadrenalinemia and therefore the likelihood that residual pathologic adrenalin-producing tissue was still present. Surgical exploration proved this to be so, and the second pheochromocytoma was found and removed.

After both pheochromocytomas had been surgically removed and the blood pressure had fallen to normal levels, the intravenous injection of 1164F was repeated, and no change in the blood-pressure level could be induced, suggesting that hyperadrenalinemia was no longer present and that all the pheochromocytoma tissue had been successfully removed.

Goldenberg, Snyder and Aranow<sup>26</sup> have devised a new test for hypertension due to circulating epinephrine. This is based on the adrenolytic effect of benzodioxane derivatives.

### TREATMENT

The treatment is surgical extirpation of the tumor or tumors, if more than one can be shown to exist. Many reports of dramatic cures have been recorded, and these have recently appeared with increasing frequency. There has been a demonstrable reduction in the operative mortality, and among the last 18 cases reviewed by MacKeith,<sup>1</sup> only 3 deaths occurred—an operative mortality of 16.6 per cent for solitary pheochromocytoma.

Ideal care before and after operation demands the assistance of an internist who, in close co-operation with the anesthetist, will carefully observe the changes in the pulse and blood pressure and regulate the dose of intravenous and intramuscular adrenalin and determine the indications for the administration of adrenal cortical extracts, both natural and synthetic. The importance of atraumatic manipulation of the tumor during operation cannot be overemphasized. The value of adequate surgical exposure is obvious, and if possible the blood supply to the tumor should be occluded before manipulation. During the operative procedure, one may be vividly impressed with the immediate dramatic fluctuations in the patient's blood pressure, because these tumors, although usually histopathologically benign, may be physiopathologically malignant. This fact is illustrated by the case report of Brunschwig and Humphreys,<sup>27</sup> whose patient had a nearly fatal attack of syncope, but finally recovered, and by the case report of Palmer and Castleman,<sup>2</sup> whose patient died before surgical treatment could be instituted.

Tumors have been successfully removed by both the extraperitoneal lumbar approach, with or without rib resection, and the abdominal transperitoneal approach. The latter probably affords a better opportunity for abdominal exploration for the presence of multiple tumors.

In the case reported above the intra-adrenal tumor was removed by a flank extraperitoneal incision, and the extra-adrenal tumor by an oblique subcostal transperitoneal approach.

### DISCUSSION

Pheochromocytoma must be ruled out as a possible etiologic agent in any patient with hyperten-

sion, whether paroxysmal or continuous and unremitting.

Perirenal insufflation of air or some other gas is at times the only nonoperative technic that will help to localize an adrenal enlargement too small to cause demonstrable displacement of the homolateral kidney.

The possibility of multiple pheochromocytomas must be considered in the management of any patient who fails to show a complete and permanent return of the blood pressure to normal after the removal of one pheochromocytoma. Multiple tumors may be present in the same patient, and more than one operation may be necessary to remove, completely, all the pathologic adrenalin-producing tissue present before one may reasonably expect the blood pressure to return to normal levels.

One of the benzodioxane derivatives, 1164F (dimethyl piperidinoaminomethyl benzodioxane), appeared to have given some diagnostic aid in suggesting the presence of hyperadrenalinemia in the case reported.

### SUMMARY

A case of coexisting intra-adrenal and extra-adrenal pheochromocytomas is reported, with a brief discussion of the surgical management that resulted in cure of the patient. This appears to be the first recorded case of surgical cure of multiple pheochromocytomas.

The clinical manifestations of pheochromocytoma are briefly reviewed, and emphasis is placed upon the variability of the symptoms and signs.

The difficulties that are at times encountered in differentiating this disease from essential hypertension, hyperthyroidism, angiospastic states, such as Raynaud's disease, psychoneurosis and diabetes mellitus are emphasized.

Importance is placed on perirenal insufflation of air as an aid in the localization of early enlargements of the adrenal gland that can be identified by no other nonoperative means.

The value of atraumatic surgical technic and of careful administration of adrenalin and adrenal cortical extracts, both natural and synthetic, when indicated, during the operation and postoperatively is stressed.

A report of the depressor effect of 1164F, a benzodioxane derivative (dimethyl piperidinoaminomethyl benzodioxane), injected intravenously, on the elevated blood pressure of a patient suffering from a pheochromocytoma is given, and the possibility that this substance will prove of help in the clinical diagnosis of hyperadrenalinemia is mentioned.

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## MEDICAL PROGRESS

### ORTHOPEDIC SURGERY

#### I Conditions of the Shoulder

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IT is the purpose of this report to present as clear-cut a clinical picture as possible of the common conditions affecting the shoulder. More than sixty articles from the literature of the past four years have been reviewed to form the basis of this survey.

Codman<sup>1</sup> so well described all known conditions that his book still represents a standard by which all that is new must be judged. Every writer on a subject pertaining to the shoulder is aware of this, and it therefore follows that anyone concerned with the diagnosis and treatment of conditions about the shoulder should be conversant with Codman's book.

Inman, Saunders and Abbott<sup>2</sup> have studied the function of the shoulder girdle by methods that are new and very promising for the future. Already their analysis of motion in the shoulder has a practical bearing. When the arm is abducted, the muscular apparatus enters into a total, combined effort—that is, the action of the deltoid and supraspinatus working together depend on a simultaneous depressor group striving to hold the head of the humerus "fulcrumed" in the glenoid, namely, the

subscapularis, infraspinatus and teres minor. This tends to disagree with the old concept that the supraspinatus initiates abduction, which the deltoid carries on. Furthermore, muscle transplants, to replace the deltoid, will not be effective, in the opinion of the authors, if there is a loss also in the power of the depressors.

During abduction of the arm, motion takes place in four joints simultaneously: the sternoclavicular, acromioclavicular, scapulothoracic and scapulohumeral joints. For the first 30° of abduction, or what is called the "setting phase," the simultaneous jockeying of these joints for position varies depending upon individual characteristics. Beyond 30° there is a rather fixed pattern in which the ratio of humeral to scapular motion is 2:1. For free and full elevation of the arm, two other conditions are necessary: lateral rotation of the humerus and rotation of the clavicle. The latter allows opening or elongation of the coracoclavicular ligaments. This has a practical bearing on fusion of the acromioclavicular joint. Since a fusion will destroy rotation of the clavicle, it will thereby limit abduction to 90° if the fusion took place with the arm at the

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side, whereas abduction will be elevated to  $135^{\circ}$  if the fusion occurred with the arm abducted

It is possible for anyone who examines the shoulder to make further use of shoulder motions in differential diagnosis if the examiner is first aware of the normal pattern. By detecting a variation from this normal pattern, attention can be focused on the particular joint involved that is disturbing the pattern. This procedure is perhaps another way of referring to what Codman<sup>1</sup> has aptly described as scapulohumeral rhythm although it is actually applicable to more joints than were originally considered. This concerns conditions about the shoulder that require careful differential diagnosis, and as a group, they can be classified as causes for painful shoulder. For the purpose of simplification, these causes are discussed below under the headings of calcifications and ruptures of the musculotendinous cuff.

In 1943, Jones<sup>3</sup> studied 600 cases of painful shoulder, and he was startled by the fact that not a single diagnosis of complete rupture of the supraspinatus tendon had been made. At the same time, he was aware that 2 per cent of all shoulders examined at routine autopsy, in patients beyond the age of thirty, showed some degree of tear of the musculotendinous cuff. Codman<sup>1</sup> observed less than 12 complete ruptures, whereas he listed hundreds of cases of incomplete rupture, and yet his own post-mortem studies revealed an approximately equal frequency of large and small ruptures. This indicates that some degree of rupture is a very common occurrence, perhaps more common than is recognized clinically. McLaughlin<sup>4-7</sup> reviewed 3000 cases of lesions of the shoulder of which 275 came to operation. This allowed him to formulate some definite opinions regarding ruptures of the musculotendinous cuff. With the addition of observations from such authors as Howorth,<sup>8</sup> Jones<sup>3</sup> and Gunning,<sup>9</sup> a clinical entity from the standpoint of the underlying pathologic lesion can now be visualized.

Probably most painful shoulders have their origin from the same anatomic fault, which is peculiar to the joint in question. In human beings the shoulder joint is at the mercy of the continuous effect of gravity. There is a rather continuous resistance to gravity by the ligaments and especially the musculotendinous cuff. In addition, the prominence of the outer periphery of the musculotendinous-cuff insertion allows it to be under continuous pressure from the drag of the deltoid. This situation leads to diminished circulatory exchange and thus to local attrition. Attrition produces a weakness in the musculotendinous cuff with the focal point over the supraspinatus insertion. If, to this picture is added excessive use, such as the maintenance of abduction positions for long periods, or faulty use, such as sudden jerky movements, a degeneration is initiated at some point within the structure of the tendon near its insertion. If faulty movements

are then continued in repeated small exertions or one large exertion, as might occur in injury, it is very simple for the tendon to give way at its degenerated point. The amount of this giving way is dependent entirely upon the location and amount of degeneration and of the force applied to the shoulder. Once the giving way has occurred, two courses seem open to nature in dealing with the lesion in the first, which forms the basis for musculotendinous tears, the attrition and degeneration may be of such extent that very little repair is attempted, the defect may remain static, and with repeated use of the shoulder, the lesion may progress, in the second, if sufficient blood supply is still available, nature may attempt to heal the degenerated area, but with repeated use and abuse, the repair process is constantly thwarted, causing an accumulation of an excessive amount of inflammatory granulation repair into which calcareous material can be deposited. This forms the basis for calcification of the musculotendinous cuff or what is commonly termed bursitis. It is possible that tears and calcification are part of the same original pathologic process based on the anatomic peculiarities of the shoulder.

#### CALCIFICATIONS OF THE MUSCULOTENDINOUS CUFF

It has been aptly stated that bursitis is no more a diagnosis than headache or jaundice, and yet the common usage seems justified because the bursa actually is secondarily involved, to a greater extent, than in cuff tears and this helps to separate the two conditions clinically.

The basic lesion has already been described but needs further elucidation. Why calcification occurs and the actual chemical nature of the calcification is not known. The fact remains that it does occur and that the location corresponds with the degenerated area within the rotator cuff. Operative findings have shown that the degree of inflammation varies in accordance with the amount of irritant material in contact with the bursal floor. This irritant material may be composed of degenerated tendon debris with or without calcification. If the same material lies deeper in the tendon, less inflammation is produced in the bursal floor, and the pain is apt to be less. However, another source of pain seems to be from tension built up within the calcareous deposit. This is borne out clinically by releasing the calcareous deposit with relief of pain. Since calcification is not always present when there is pain, the pain must be produced by inflammation of the bursal floor secondary to degenerated tendon debris. In this type of case needling is apt to be less efficacious. The pain that is present depends upon the amount of inflammation and the tension within the calcareous deposit. There is little correlation between the clinical and roentgenographic features of the disease.



It has been shown that degeneration can occur with diffuse deposition of calcium without evidence of a tear. On the other hand, it is common to find degeneration, inflammation and calcification in the presence of tears. This indicates that bursitis and tears commonly coexist and that the clinical differentiation must be on the preponderance of tendon disruption (internal derangement), which persists, versus inflammation and calcium deposition, which may or may not persist. Histories of repeated attacks of painful shoulder for periods as long as ten to fifteen years are often obtained, but autopsy findings have shown that calcification is rare after sixty-six years of age, whereas cuff tears, without surrounding inflammation, are not uncommon. The basic reason for the reversibility of bursitis as compared with cuff tears is unknown.

It is well known that the relief of pain from an acute attack may spontaneously occur, and although repeated attacks may supervene, the disease is eventually self-limited unless associated with tears that persist. Because of the frequency of spontaneous relief (the actual percentage is unknown) it becomes difficult to evaluate benefits of treatment. The only difference between acute and chronic lesions is the degree and extent of inflammation and the consistency and tension of the material in the deposit.

Treatment can be considered either curative or palliative. In any case one must first determine whether symptoms, by reason of their severity, duration and cause for disability, warrant curative or palliative procedures. The only curative procedure is generally agreed to be operative, and the operation is usually accomplished with a small muscle-splitting incision through the anterior deltoid muscle and evacuation of the calcareous deposits with excision of the degenerated portion of the tendon. A simple sling, mild heat and exercises will then tend to restore the arm to normal, usually within a period of two or three weeks, the pain will have subsided, and within six weeks the motions will be restored.

Palliative procedures are variable and somewhat more difficult to evaluate. The more frequent of these is needling of the lesion under local anesthesia. In needling, an attempt is made to reach the calcareous deposits and remove as much as possible through the needle. This is sometimes facilitated by the use of saline solution to dilute the deposit. X-ray examination, at times, is a helpful guide to be sure that the needle is within the confines of the deposit. Some authors believe that by perforating the tendon overlying the deposit, sufficient material will escape through the puncture wound to effect relief of pain. It seems reasonable that the needling method can in no way rid the tendon of its degenerated area.

Many authors have advised x-ray therapy, the usual dose being approximately 150 r at 8 ma

200 KV through 1.5 mm of copper, in addition to 1 mm of aluminum filter with a 50-cm target-skin distance. One to three such doses over a period of one week are necessary. All advocates of this method indicate good results in acute bursitis, but the follow-up studies are not of long enough duration and sufficiently detailed to include the time for recovery, the amount of motion gained or the number of calcific deposits eradicated. It therefore remains unsettled whether x-ray therapy actually relieves a greater percentage than if the disease is left to spontaneous recovery. Perner<sup>3</sup> advises the use of intravenous iron cacodylate as a curative agent.

#### RUPTURES OF THE MUSCULOTENDINOUS CUFF

Because of the similarity of underlying lesions of the musculotendinous cuff, it is difficult to differentiate tears from bursitis, but certain points should be kept in mind as being helpful. If cases are analyzed for type of pain, residual-motion defects and the course of the complaints, it should be possible to tell one from the other in most cases. It seems reasonable from the foregoing that in the acute stages, diagnosis may be quite impossible. Furthermore, it is quite unnecessary to make an accurate diagnosis in the early phase of rupture because the lesion is an old one to start with, and the treatment will be no more effective if done early than late. This disagrees somewhat with Codman,<sup>4</sup> who insisted that tears should be operated upon from the moment of their diagnosis, preferably in the acute phase. Once the acute phase has passed, the signs in the shoulder will become somewhat clearer. As a rule, there will be no continuous pain, but rather the complaint will be that of discomfort on a certain motion, particularly at a definite point in the arc of that motion.

Upon examination there will be much less limitation of passive motion than would be expected. Scapulohumeral rhythm will be disturbed. Inability to initiate abduction is not a good diagnostic sign because the remaining musculotendinous cuff may exert sufficient depressor effect to enable the deltoid to carry out abduction. Perhaps a better test would be to determine the inability to maintain abduction against resistance, with the arm first in external and then in internal rotation. In this way, the lesion may be more accurately placed in the anterior or posterior quadrant of the musculotendinous cuff. At times, local palpation may reveal a sulcus if the tear is sufficiently large, or there may be a comparatively painless click when the torn portion slides under the acromion. These signs, when present, are helpful but in no way completely diagnostic. At times the diagnosis can be made only by surgical exploration. The only indication for surgery, however, is for pain or disability sufficient to make such a procedure worth while from the patient's point of view.



It is quite generally agreed that the majority of minor tears heal spontaneously under conservative treatment. It is more likely that the minor lesions heal in spite of treatment, and because many do heal, it is wise in any given case to use a therapeutic trial of conservatism. Should the symptoms continue to the point where the patient seeks further treatment, it is generally agreed that the only effective treatment is surgical. The actual surgical attack is about as varied as the number of surgeons describing it.

McLaughlin<sup>6, 7</sup> has described an exposure with the skin incision paralleling the suspender line just lateral to the acromioclavicular joint. The acromion is then osteotomized to give adequate exposure of the shoulder cuff. This has the virtue of avoiding the nerve supply to the deltoid. It has the added advantage of removing the acromion if this is deemed necessary to give the repair more room.

A second approach is the anterior deltoid splitting, which can be enlarged by releasing the upper attachment of the deltoid from the acromion if it becomes necessary. Care must be exerted in the use of this incision to avoid injury to the axillary structures during medial retraction, and occasionally, some of the nerve supply may be lost to the anterior fibers of the deltoid.

In either approach, once exposure has been accomplished, the attention is directed to locating the tear. Most of the time, this will not be difficult if the operator is aware that incomplete tears may not be visible from the surface. In such cases, by creating an opening at the periphery of the cuff in the area under suspicion, the tear can be located. Tears of the rotator cuff are so varied that no two are alike, but in general, they are either transverse near the insertion of the cuff or longitudinal, usually between the tendon of the subscapularis and supraspinatus. It is sometimes difficult to visualize in which direction the initial tear might have started because there is a tendency, with continued use of the shoulder, for the tear to progress and the edges to retract. What appears to be a longitudinal tear may have started as a transverse one.

Once the tear has been visualized, it becomes an individual problem to determine the type of repair. In general, the small tears can be resutured to their original point, especially the transverse variety, by mattress sutures through the bone. The longer retracted tears may require side-to-side repair to avoid tension. Capsular flaps, such as that described by Jones,<sup>8</sup> may be helpful in repairing this type of defect. At times the retraction may be such that end-to-end apposition cannot be obtained, and the torn edge may need transplantation to the head of the humerus at a point more medial than the original insertion. In any event, the postoperative care will be quite similar in all cases, taking into account the amount of repair necessary. Three to six weeks are allowed for tissue healing, and the

affected arm is immobilized in a sling. Active exercises are then started, and usually within a period of three months, shoulder motions will be restored. In severe tears such as complete avulsions of the entire cuff, motions will be restored to 50 per cent of normalcy. In some cases, certain authors have advised shoulder fusions for these severe injuries. On this point there is no unanimity, and the solution should remain an individual one in each case.

#### PERIARTHRITIS

Quite apart from bursitis or rotator-cuff tears, a clinical entity that occurs in the shoulder has been discussed by authors such as Tarsy,<sup>10</sup> Wilson,<sup>11</sup> Neviaser<sup>12</sup> and others<sup>13, 14</sup>. Codman<sup>1</sup> referred to this group as tendinitis of the rotators. Wilson described it as periarticular adhesions, and it has been referred to as adhesive capsulitis. The actual cause of this condition is unknown, but because it occurs with such uniformity between the ages of fifty and fifty-five, particularly in women, it is suggestive evidence that there is an underlying endocrine imbalance. Against this hypothesis is the fact that it usually remains localized to one shoulder.

Several points set this lesion apart from other shoulder conditions. Upon exploration the subacromial bursa has usually been found uninvolved, tears and calcifications are very infrequent, there has been general fibrosis, which fixed the periarticular structures at their insertions, limiting not only direct shoulder motion but also scapulothoracic motion, there are seldom localized areas of discomfort, but instead, the entire shoulder seems tender and painful, x-ray films, as a rule, show nothing other than decalcification, and there is an absence of traumatic history. In follow-up studies practically all these shoulders become normal within an average period of two years, and certain experiences have led away from surgical treatment. In a follow-up study reported, the rehabilitation period in 34 patients averaged five months. This was accomplished by repeated novocain injections either locally or as block anesthesia combined with repeated careful mild manipulations, as well as daily exercises on the part of patients. In addition to local treatment, particular attention is paid to general therapeutics, correction of endocrine disorders and so forth.

#### FROZEN SHOULDER

Throughout the literature, the use of the term "frozen shoulder" carries only the connotation of a shoulder that has lost entirely its active and passive motion. Many conditions have been described as a cause, such as bicipital tenosynovitis, subacromial bursitis, partial and complete ruptures of the rotator cuff and dislocations and elongations of the biceps tendon. Lippmann<sup>15</sup> pointed out that bicipital tenosynovitis is a common cause, and he explored 32 cases of frozen shoulder. All showed inflammatory changes of varying degree in the

biceps tendon and sheath, and only a few showed bursal lesions. Tarsy,<sup>16</sup> on the other hand, tried to separate each of the above conditions as clinical entities, but the symptoms and signs are not clear-cut so that in the present state of knowledge, these diagnoses may apply when the condition does not fit the well known entities. It is also possible that they represent complications or extensions of the inflammatory process accompanying bursitis and cuff tears.

#### RECURRENT DISLOCATION OF THE SHOULDER

The writings of several authors, including Henderson,<sup>17</sup> Gray,<sup>18</sup> Bost,<sup>19</sup> Wellington,<sup>20</sup> Magnuson,<sup>21</sup> Crosby<sup>22</sup> and others, have been reviewed in an effort to find out if there has been any clarification regarding the causative factor in recurring dislocations of the shoulder. Practically all reiterate Bankart's conception that an injury to the glenoid ligament is an essential factor in allowing dislocations to occur. Magnuson<sup>21</sup> has added the concept that there is a lack of muscle balance, which fails to resist the downward and forward displacement of the head, and hence he has outlined the restoration of this balance by shifting the subscapularis muscle.

The surgical procedures advised for the correction of recurrent dislocations are varied, but in general, the once popular Nicola procedure has lost some favor because the tendon frays off when put to hard usage. There still seems to be a place for the Nicola<sup>23</sup> procedure except in patients who are expected to make vigorous use of their arms. Bankart's operative repair is quite generally accepted. However, it is subject to modifications such as the addition of reinforcing fascia or osteotomy of the glenoid. In general, it seems that there is no selection of choice and that the operator, in each case, must repair what seems necessary after noting the defects present at the time of operation. There are very few adequate follow-up series to help in the selection of operative procedures. In cases followed for more than one year, Henderson<sup>17</sup> reported a 91 per cent cure using his own tenosuspension operation. Shepherd<sup>24</sup> strongly urges the search for loose bodies in each case of repair for recurring dislocations. In old dislocations that are irreducible, Steindler<sup>25</sup> has advised arthrotomy, with replacement of the head and reconstruction of the capsule.

#### ACROMIOCLAVICULAR DISLOCATIONS

There is no unanimity of opinion regarding the diagnosis or treatment of dislocations of the acromioclavicular joint. Most authors, however, agree that dislocations of this joint can be partial, when the acromioclavicular ligaments are torn, or complete, when the coracoclavicular ligaments are torn. In partial dislocation many types of conservative fixation are advocated, such as a modified Lever-type sling by Goldberg,<sup>26</sup> a strap brace advocated by

Giannestras<sup>27</sup> and a webbing strap shoulder spica as described by Wolin.<sup>28</sup> No one has presented a good picture of end-results comparing the treated with the untreated partial dislocations. This perhaps accounts for the fact that these many methods of treatment are about equally successful. Only an occasional case of partial dislocation is disabling. Bloom<sup>29</sup> advocates early reduction in all cases and maintenance of reduction by wires to give fixation while the ligaments are going through their primary repair. These wires are removed two months later. Bloom, following this form of treatment, returned 12 men to full military duty, but in his opinion it would take a considerable series of treated versus untreated dislocations to prove that the primary treatment in all cases should be routine wiring. Urist<sup>30</sup> found that conservative treatment led to a stable painless joint in 80 per cent of partial dislocations.

Soule<sup>31</sup> has pointed out how x-ray films may be taken to demonstrate mild or severe acromioclavicular separations. With an anteroposterior roentgenogram of both shoulders taken in the upright position with a 20-pound weight in each hand, widening of the involved joint and elevation of the acromial end of the clavicle will be demonstrated. The mere presence of a demonstrated separation does not preclude surgical treatment unless it in some way interferes with the efficiency of the patient, and there are many reported methods of surgical attack to restore the patient's efficiency. Mumford<sup>32</sup> believes that the clavicle, either as a whole or in part, may be excised without impairment to the shoulder girdle. He recommends excision of the distal 2.5 cm of the clavicle for painful recurrent separations or for chronic arthritis of the acromioclavicular joint. In his hands, 9 cases resulted in satisfactory function with freedom from pain. Urist<sup>30</sup> agrees that this treatment will give a painless shoulder, but strength will not quite equal that of the normal shoulder.

Other forms of treatment have been discussed toward stabilizing the joint. Birkett<sup>33</sup> reported a repair with fascial strips, and follow-up x-ray studies revealed considerable ossification of the new fascial ligaments, the patient had stability and strength of the shoulder with some limitation of scapular and arm movements. Soule<sup>31</sup> has reported similar ossification as early as twenty-two days after injury. He further states that if ossification has not appeared within six weeks after injury, it was not noted in subsequent examinations. Furthermore, the ossification did not seem to bear any relation to type of treatment or to contribute to any disability but actually might aid in restoring continuity of the damaged ligament.

#### MISCELLANEOUS CONDITIONS

Much has been written regarding the treatment of injuries about the shoulder joint, especially as an outcome of the experience in World War II. There

is nothing particularly new that does not relate to similar injuries elsewhere. Parnall<sup>34</sup> has reported a reconstruction in 2 cases in which there was gross shell destruction of the shoulder joint. The lack of adequate follow-up study has kept such reports from being instructive, although they are very interesting. Pendergrass<sup>35</sup> has given a discussion of neuroarthropathies as they pertain to the shoulder that well sums up what is presently known regarding such conditions. Camiel<sup>36</sup> has presented an excellent description of the progressive x-ray findings in tuberculosis of the shoulder and has attempted to correlate the x-ray with the clinical findings. He believes that no individual x-ray sign is pathognomonic but that, when the films are taken in progressive sequence, the diagnosis will be apparent. Hendricks<sup>37</sup> has reviewed the scalenus anticus syndrome and reported 4 cases. The point of most importance and interest regarding the shoulder joint is the exclusion of the shoulder in the differential diagnosis by the finding of no tender points and a normal range of motion.

Regarding diseases about the shoulder joint, such as arthritis, sepsis and tumors, there is very little new that is of interest. Smith-Petersen<sup>38</sup> has advised acromioplasty as a surgical procedure in rheumatoid arthritis. This is particularly indicated for removing a source of pain and thereby for allowing freer use of not only scapulohumeral but also scapulothoracic motion.

Rowe and Yee<sup>39</sup> have described a posterior approach to the shoulder joint, and McKeever<sup>40</sup> has covered in detail the problem of amputations and prostheses for the upper extremity.

\* \* \*

In conclusion it should be apparent to all that in the differential diagnosis of painful conditions about the shoulder joint, the examiner must be constantly aware of distant lesions which produce radiation pain to the shoulder. Anyone interested is referred to a discussion of this problem by Bosworth.<sup>41</sup>

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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### CASE 34201

#### PRESENTATION OF CASE

A thirty-two-year-old woman entered the hospital complaining of occipital headache and increasing drowsiness.

Eight years prior to admission a diagnosis of pulmonary tuberculosis was made by x-ray and sputum examination. The patient was treated by artificial pneumothorax for five years, after which the sputum was negative and the disease was thought to be arrested. Sixteen months before entry she began to have steady pain in the left lower quadrant. Two months later an abdominal operation was performed at another hospital, and a "mass of adhesions" was found. No organs were removed. The patient seemed to improve, but six months before admission a mass appeared in the left lower quadrant. This was diagnosed as a pelvic abscess, and was incised and drained at still another hospital. Cultures of the pus were negative. Guinea-pig inoculation was not done. A fecal fistula developed and drained intermittently up to the time of admission. Eight days before admission the patient complained of a heavy feeling in the head, and had a temperature of 102°F. Two days later she developed occipital headache, followed by nausea, increasing drowsiness and diplopia. Her physician found that the temperature was normal, and no neck rigidity was present.

On physical examination the patient was very drowsy, apathetic and slow to answer, but oriented and coherent. The heart and lungs were normal. There was a midline suprapubic scar with a 3 mm opening discharging small amounts of greenish-brown liquid and soft, solid material, which resembled feces but was odorless. Pelvic examination revealed a moderately tender mass about 12 cm in diameter, apparently consisting of uterus and adnexa matted together. The neck was not stiff, and there was no Kernig sign. The vision, fundi and visual fields were normal. The pupils were 1.5 mm in diameter and equal, and reacted to light and accommodation. There were no gross ocular palsies, but upward gaze seemed somewhat limited. Convergence was good. There was diplopia on looking in any direction except upward.

One examiner noted slight weakness of the right external rectus muscle. The facial muscles were thought to be slightly less active on the right. Hearing was reported by several different examiners to be diminished on the right, but quantitative tests were not done and Rinne and Weber tests were negative. Other cranial nerves were normal. Motor findings were normal. The tendon and abdominal reflexes were normally active and equal, and plantar reflexes were normal. Sensation was normal.

The temperature was 98.6°F, the pulse 80, and the respirations 20.

Examination of the blood disclosed a hemoglobin of 15 gm and a white-cell count of 25,000, with 85 per cent neutrophils. The blood non-protein nitrogen was 23 mg., the total protein 8.12 gm and the fasting blood sugar 112 mg per 100 cc. The blood Hinton test was negative. Repeated urine examination and urine cultures were negative. The spinal-fluid pressure was equivalent to 260 mm of water, with normal dynamics. The fluid contained 64 white cells per cubic millimeter, with 72 per cent lymphocytes, 15 per cent polymorphonuclear leukocytes and 12 per cent monocytes, the total protein was 116 mg and the sugar 120 mg per 100 cc., and the chloride 124 milliequivalents per liter. The colloidal-gold wave was 2223333111,

and the Wassermann test was negative. A guinea-pig inoculation was negative.

X-ray study of the chest showed numerous linear areas of increased density in the right upper lobe and, to a slight degree, in the left midlung field. There was no evidence of cavitation. Skull films were normal. An electroencephalogram showed high voltage and slow waves bilaterally, most prominent in the frontotemporal and parietal regions and probably somewhat more marked on the left. Streptomycin was given intrathecally (50,000 units twice a day) and intramuscularly (0.4 gm every six hours). Penicillin was given intramuscularly (50,000 units every three hours).

During the first week the patient did not improve. The temperature remained normal. Drowsiness and headache became more pronounced. Moderate rigidity of the neck and a positive Kernig sign were present. The margins of the optic disks were slightly blurred. On the sixth and seventh days weakness of the left arm and leg developed. The tendon reflexes were active and equal, and the plantar reflexes were normal. Bilateral occipital burr-hole exploration on the seventh hospital day was negative, and a ventriculogram was normal. The cerebrospinal-fluid pressure remained above 300 mm, and two days later a right subtemporal decompression was performed in an attempt to relieve the increased intracranial pressure. On the next day the left hemiparesis improved, and the right became less drowsy. On the fifteenth hospital day coarse nystagmus on right lateral gaze was observed. This cleared up during the next week. During the next six weeks there was slow improvement, the mental status became normal, and the patient was able to sit in a chair. She complained of slight dizziness, but there was no vertigo. The temperature remained normal. Approximately two months after admission, the patient was able to stand and walk without difficulty. She continued to have mild headaches. The tendon reflexes were very brisk, and there was bilateral ankle clonus, but neurologic examination was otherwise negative. Streptomycin, intrathecally and intramuscularly, and penicillin were given without interruption. During the next few days the area over the subtemporal decompression became tense and bulging. The spinal-fluid pressure rose to over 300 mm, and headache, accompanied by vomiting, increased steadily in severity. Seventy-one days after entry the patient was found dead.

#### DIFFERENTIAL DIAGNOSIS

DR RAYMOND D ADAMS\* May we see the x-ray films?

DR STANLEY M WYMAN Films of the chest show a rather extensive process involving the right upper lobe, with considerable retraction and collapse of the right upper lobe, the hilus being dis-

placed inward. There is also a linear area of fibrotic density in the left midlung field and the left first interspace. The heart shadow is not remarkable. The diaphragm is symmetrical. The spleen is rather large, within the upper limits of normal in size. One cannot exclude activity in the pulmonary process. Films of the skull, I believe, show the posterior clinoids to be a little sharper than usual, and there is a suggestion that the right posterior clinoid is eroded on two films. Air studies are incomplete and not ideal. They show no gross dilatation or displacement of the ventricular system.

DR ADAMS There is no evidence of a destructive process in the mastoid region? There is nothing to suggest a tuberculous infection of the medulla or mastoid cells?

DR WYMAN No, I think that the mastoid cells are well aerated from the available films. There is no evidence of acute bone destruction or erosion.

DR ADAMS It seems from the data submitted that we must assume the patient had tuberculosis. This was established by x-ray films of the chest, sputum examination and the later development of a sterile abscess in the pelvis and of a fecal fistula. The pain in the left lower quadrant, which appeared sixteen months before entry, was probably the first manifestation of tuberculous salpingitis. There is no mention of either gastrointestinal or genitourinary symptoms, but since the pain was in the left quadrant, salpingitis is more likely than tuberculous infection of the descending colon. Tuberculosis more often involves the ileum or cecum, and if this had happened, the pain would have been periumbilical or in the right lower quadrant. Moreover, if a tuberculous ulcer had eroded through the bowel wall to give the pelvic abscess that was found later, it should not have been sterile, colon bacilli should certainly have been cultured. I am unable to settle the point whether the pelvic abscess came from the fallopian tube or the bowel.

The symptoms that appeared during the last phases of the illness were clearly neurologic. The occipital headache, drowsiness and nausea are the first indications of this central-nervous-system extension and could be explained by meningeal irritation as in a leptomeningitis or by a space-consuming lesion in the posterior fossa. The cerebrospinal fluid does not entirely decide which of these two mechanisms was operative. There were pleocytosis and elevation of protein, meaning in all probability that there was some localized or diffuse meningeal inflammation, but the elevated blood sugar is against a bacterial infection in the subarachnoid space. With such an infection, the cerebrospinal-fluid sugar would have been low—below 40 mg per 100 cc. Elevated cerebrospinal-fluid sugar is always related to a high blood sugar, either from diabetes mellitus or, as in this case, with no glycosuria, from injection of glucose intravenously. The cerebrospinal-fluid pressure was

\*Assistant professor of neurology, Harvard Medical School.

elevated, and I am therefore inclined to explain at least part of the patient's drowsiness, slowness in response and apathy, as well as the slow waves bilaterally in the electroencephalogram, on the basis of elevated intracranial pressure. In view of the absence of stiff neck and the findings in the cerebrospinal fluid, I assume that there was a local meningeal infection but not a diffuse tuberculous meningitis.

Are there any neurologic findings that give us a clue to the location of this pathologic process? There are. The right abducens muscle was weak, and the patient had diplopia quite early in the illness — before, I should think, it would have developed as a false localizing sign of increased intracranial pressure. The tests of ocular movement are not well worked out, but I suppose that she had a partial right-sixth-nerve palsy. The right-facial-muscle weakness points to involvement of the seventh cranial nerve, and the partial deafness, about which there was some doubt, to the right auditory nerve. Later there were a left hemiparesis, which cleared up after a few days, and nystagmus on looking to the right. All these symptoms indicate a lesion in the lower pons on the right side, probably in the middle cerebellar peduncle, which disturbed the function of but did not directly invade and destroy the right sixth, seventh and eighth cranial nerves in their intrapontine course, the vestibular nuclei and the right corticospinal tract. A slight inco-ordination of the right arm and leg is all that I need to complete the picture for a cerebellopontine lesion. The absence of ataxia, I suppose, means that involvement of the cerebellar peduncles or hemisphere was not extensive. It must be admitted that the left hemiparesis, which disappeared after the right subtemporal craniotomy, could have been due to a lesion in the right internal capsule or posterior part of the frontal lobe. The cranial-nerve palsies would then have been unrelated.

Up to this point I have persuaded myself that the patient had generalized tuberculosis, not miliary, and that the recent development consisted of a tuberculoma in the lateral part of the lower pons or possibly here and in the right frontal lobe, which produced some elevation of intracranial pressure and localized inflammation of the adjacent leptomeninges. I assume that the physicians who were responsible for this woman's care were of the same opinion because they took the trouble to inoculate a guinea pig, which remained healthy, and proceeded to administer streptomycin. The ventriculogram was probably done to obtain more information regarding the locality of the disease and the temporal craniotomy.

Are there any other diseases that could produce this same clinical picture? Yes, two other possibilities must be considered. Torula may be combined with tuberculosis. One of our patients had

pulmonary tuberculosis and lymphadenitis, established by biopsy and culture, and then developed a torular infection of the lungs and meninges, which proved fatal. The cerebrospinal-fluid changes are very similar to those in tuberculous leptomeningitis except that the cultures are repeatedly negative for tubercle bacilli and the fungus can be seen or cultured. In the case under discussion the abdominal lesion and the fecal fistula are against torula.

The other possibility is that a mixed bacterial infection developed in a patient who already had tuberculous lesions. Either the lung or the pelvic abscess could have been secondarily infected by other pyogenic bacteria. The brain lesion or lesions would then have been metastatic abscesses. In our pathological material we recently had a case of pulmonary tuberculosis in which there was a subsequent development of hemiplegia and signs of increased intracranial pressure and of meningeal irritation. The neurologic signs were found at autopsy to be caused by a large putrid abscess in the left frontoparietal region. There was a mixed flora of bacteria in the abscess, — fusiform bacilli, spirochetes and an anaerobic streptococcus. I can neither affirm nor deny this possibility in the case under discussion. I suppose that if the cerebrospinal fluid had on repeated examinations contained a normal sugar, one would have had to think seriously of this possibility, but without knowing the subsequent cerebrospinal-fluid findings I would not venture this diagnosis.

Tumor of the lung, with metastases to the brain and other organs, is a remote possibility.

#### CLINICAL DIAGNOSIS

Tuberculous meningitis, probable

#### DR ADAMS'S DIAGNOSES

Pulmonary tuberculosis  
Generalized tuberculosis, with tuberculous salpingitis  
Fecal fistula  
Tuberculoma, right pons and cerebellar peduncle and ? left frontal lobe  
Tuberculous meningitis

#### ANATOMICAL DIAGNOSES

*Pelvic abscess*  
*Brain abscesses, multiple*  
Pulmonary tuberculosis, healed  
Operative wounds — subtemporal decompression, ventriculogram, appendectomy, old

#### PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: The systemic findings at autopsy were comparatively few. There was a good-sized tubo-ovarian abscess, and the small

bowel had become adherent to it. There was a closed fistulous tract between the small bowel and the anterior abdominal wall. I think it possible that that fistula never drained. That is perhaps the reason why there was no culture. We could find no evidence of tuberculosis in the walls of the abscess, and the lung showed minimal evidence of tuberculosis — no cavity and only a fibrous scar at the site where the lesion had been, and a little compensatory emphysema.

Dr. Kubik will tell the rest of the findings.

DR. CHARLES S. KUBIK: At autopsy there were signs of generalized increased intracranial pressure in the form of flattening of the cerebral convolutions, cerebellar pressure cones and enlarged ventricles. There was no visible generalized, subarachnoid exudate over the brain or spinal cord, — not even a definite thickening or cloudiness of the arachnoid membrane, — but there was a prominence of the inferior portion of the right cerebellar hemisphere, which was soft and fluctuant and turned out to be an abscess. Projection of the cerebellum into the foramen magnum — that is, a cerebellar pressure cone — unquestionably caused compression of the medulla and death from respiratory paralysis. There were also small abscesses in the right frontal lobe. All the abscesses had thick capsules, indicating that they had been present for some time, a matter of weeks at least. The cavities were filled with thick, greenish-gray pus. There were no tubercles either in the meninges or in the walls of the abscesses, and tuberculosis can be ruled out by the gross and microscopical findings. Smears were negative, and I was not able to find any organisms in sections of the abscesses or of the meninges.

DR. MALLORY: One anaerobic culture from one of the brain abscesses grew colon bacilli. It is a very unsatisfactory organism to find, since one never knows how to interpret it.

DR. KUBIK: Perhaps more attention should have been paid to the nystagmus, weakness of the sixth and seventh nerves and diminution of hearing, but apparently these signs were not very definite. The only explanation we have for the hemiparesis is the large abscess of the cerebellum pressing against the medulla. I do not believe that the small abscesses in the right frontal lobe could have accounted for the left-sided weakness that was present for a while and later apparently subsided. The ab-

scesses were multiple, unquestionably metastatic, and the only possible source that was found was the infection in the pelvis, though metastatic abscesses of the brain from other regions than the lungs are rare. There were no definite abnormal findings in the spinal meninges, spinal cord or nerves of the cauda equina, resulting from the prolonged use of large quantities of streptomycin.

## CASE 34202

### PRESENTATION OF CASE

A twenty-three-year-old man entered the hospital complaining of severe shortness of breath.

He was discharged from the Army one and a half years before entry, when no abnormalities were noted. He was apparently well until three months prior to admission when he began to notice poorly localized and shifting pain in the right side of the chest, without radiation to the shoulders. Soon he began to have profuse night sweats but had no cough, hemoptysis or dyspnea. About three weeks before entry he developed shortness of breath upon exertion. This symptom rapidly increased in severity so that he slept very poorly at night, and he had to sit up in bed to breathe. A physician found fluid in the right side of the chest, and a subsequent thoracentesis produced about "a quart" of bloody fluid. An x-ray film taken after removal of the fluid showed a questionable tumor of the lung. Although the dyspnea was somewhat relieved by the thoracentesis, other symptoms, such as epigastric fullness, anorexia and brief bouts of diarrhea, began to occur. The patient had lost 15 pounds in the two previous months. He denied any contact with tuberculosis.

Physical examination showed a well developed and well nourished man who was mildly dyspneic while sitting up in bed. No superficial lymph nodes were palpable. There was an acneform rash over the chest and back. There was flatness over the lower two thirds of the right lung field, and breath sounds were absent over this area. Coarse breath sounds were heard at the right apex. The left lung was clear to percussion. The rest of the examination was negative.

The temperature was 98°F, the pulse 90, and the respirations 24.

Examination of the blood revealed a red-cell count of 5,120,000, with a hemoglobin of 13.6 gm., and a white-cell count of 17,800, with 74 per cent neutrophils, 22 per cent lymphocytes and 4 per cent monocytes. The urine was normal.

Review of the x-ray films taken at another hospital and those taken on admission showed a massive, right-sided pleural effusion, with a shift of the mediastinum and heart to the left. Bucky films revealed a complete collapse of the right lung, the lateral border of which appeared lobulated. The right main bronchus was seen to a point about 2.5 cm. below the carina, where it ended abruptly. There were several areas of increased circular density, varying in size from 1 to 1.5 cm. in diameter, overlying the collapsed lung and farther out in the region of the eighth rib posteriorly. The diaphragm was not seen on the right. The left lung was well aerated, and no changes were noted in its parenchyma.

On the day after admission an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR CARROLL C MILLER. One immediately jumps to the query, What was the operation performed? It is extremely unlikely, in this hospital at least, that a thoracotomy would be performed on a patient the day after admission unless for an emergency condition. My assumption is that the operation was a bronchoscopy, which should be included as a part of the investigative program.

The highlights of the data given are quickly summarized. In the past history we have a short period of illness. The patient was apparently well on discharge from the Army one and a half years before admission, and the first sign of illness presumably occurred only three months before he was seen here. As a bit of negative evidence he had no contact with tuberculosis. This, of course, may be of equivocal value. In the present illness the salient facts are pain in the right side, night sweats, dyspnea, disturbance of the gastrointestinal tract, with anorexia, epigastric fullness, diarrhea, weight loss, bloody fluid in the chest and the question of a tumor in the lung. Two interesting and probably important negative data are no history of cough and no hemoptysis. When the patient was admitted examination showed signs of fluid in the right side of the chest. There were signs of con-

solidation or perhaps of transmission of tracheo-bronchial breath sounds at the right apex. On the unaffected side again there were no palpable lymph nodes. The left lung was clear. The abdominal examination was presumably negative. The laboratory data do not indicate much except a mild hypochromic anemia and a definite leukocytosis without significant elevation of neutrophils. The x-ray films show effusion, an apparently lobulated lung, bronchial obstruction and areas of circular density overlying or perhaps in the right lung. The left lung was normal. May we see the x-ray films?

DR STANLEY M. WYMAN. I am sorry I cannot demonstrate all that the record describes because the most valuable films were those taken immediately after the removal of the fluid. The areas of density described in the lung are not visible on these films. All we can see is a massive effusion with a fluid level at this point and the collapsed rim of upper lobe, which appears to be normal in thickness and contour. There is no appreciable thickening of the pleura in this region. The heart and mediastinum are displaced toward the left. There is a poorly seen area of round density lying behind the heart on the left side, to the left of the spine. I do not believe this is accounted for entirely by the aorta. The patient was a young man, and I would not expect the aorta to have this wide sweep. Recalling the film taken at the other hospital, which I happened to see, I was not impressed by the obstruction to the bronchus described in the record, and I am not too sure that it was a valid finding.

DR MILLER. Could this line be the left pleura pushed over by a mass in the mediastinum or arising from the right side of the chest?

DR WYMAN. I think so. The left lung is clear. There is no bony disease on the left. On the right it is impossible to exclude it. The later film shows no defect in the bones. The film taken in the upright position shows air in the pleural cavity, and there is now a suggestion of some thickening of the parietal pleura.

DR MILLER. From the description of these x-ray films, should I minimize to a certain extent the report about bronchial obstruction seen on the films taken elsewhere and also the areas of circular density?



DR WYMAN I would not minimize the latter I think they were present. There were nodular densities that appeared to be over the surface of the lung rather than actually inside it. I cannot demonstrate them on these films.

DR MILLER At any rate, they were clearly seen and may be evidence of extension or metastases from a tumor or some other process outside the primary focus.

Let us analyze the symptoms and signs from a positive standpoint. This patient started out with pain in the right side of the chest. This may have been pleurisy — dry at first. Was this a pleurisy-like pain? The description given in the record does not say. The pain may have been due to invasion of nerve trunks in the mediastinum or chest wall. I cannot explain the shifting nature of the process on the basis of either pleurisy or tumor involvement. It is true that pleurisy very frequently jumps from one place to another but certainly is not likely due to movement of fluid. The patient's dyspnea may have been due to the accumulation of fluid in the right side of the chest or to some degree of bronchial obstruction leading to collapse of the lung on that side. He had a 15-pound weight loss. This may have been caused by infection or a malignant lesion. He had a bloody pleural effusion. Serous effusion due to systemic disease, such as a cardiorenal condition, would not be bloody. If this was an infectious process, the most likely diagnosis is tuberculosis. It is comparatively rare for the ordinary effusion of intrapulmonary tuberculosis to be bloody. The incidence of bloody effusion with tuberculous pleuritis, on the other hand, is notable. Infarction of the lung could have caused a bloody effusion, or irritative factors in the pleural cavity may have accounted for an outpouring of first serum and then blood, particularly an embolus from a malignant tumor. Apparently, at one time at least, there was some degree of bronchial obstruction. If this was so, the obstruction may have been intrinsic, or due to a foreign body. I believe we can throw that out immediately because of the lack of a positive history. Or it may have been intrinsic tumor. Extrinsic pressure from a tumor mass, or intrinsic tumor, might well account for bronchial obstruction. The leukocytosis may have been on the basis of infection, although there was not the usual elevation of the

neutrophil count. Necrosis of tumor frequently causes elevation of the white-cell count.

This case is interesting to me because of the lack of respiratory symptoms, particularly cough. It is unusual to have obstruction of the bronchus, whether from intrinsic or extrinsic causes, not accompanied by cough. I should guess that the first respiratory distress occurred because of pressure of fluid on the lung. What diagnosis, therefore, can we entertain? In the first place, we can consider briefly, and let it drop promptly, the matter of vascular anomalies, such as congenital arteriovenous fistula. This probably should have been picked up by previous history and previous x-ray studies. These patients invariably have pathognomonic signs, and none were mentioned in the history or physical examination. We may think of parasites, such as the echinococcus, or fungi-like actinomycosis, but again we do not have fever or signs of irritation within the lung. The patient was apparently well until recently. I feel fairly confident in ruling out intrapulmonary tuberculosis because of the bloody pleural effusion.

Under the heading of tumors he may have had a primary bronchiogenic carcinoma. This patient was a young man, younger than the age group in which we usually find carcinoma of the lung, but it should be considered. Could he have had metastatic disease of the lung from some other source? Possibly. He had gastrointestinal symptoms, he may well have had gastric carcinoma. Again, he was young for that type of disease. Most likely of all the tumors, I believe, is sarcoma, because it occurs most frequently in the younger age groups. I believe that it is impossible to determine the nature of the sarcoma with the data at hand, but it may have been fibrosarcoma, it may also have been neurogenic fibrosarcoma or neuroblastoma. I do not believe that I can go farther than to say that he had a sarcoma.

We have, then, a young patient with a rapidly progressive disease characterized by pain, bloody pleural effusion and a lesion, which I believe was a malignant one, and the most likely diagnosis is sarcoma arising in the mediastinal tissues to produce pleural irritation and some degree of obstruction to the right main bronchus.

DR DONALD S KING We saw this man in the Thoracic Clinic and now that primary cancer of the pleura has been restored to good standing in

this hospital, we suggested that it might be that. That was one of the guesses raised at that time, — whether it was that type of growth. Lack of actual lung symptoms is one of the things that Dr. Miller has brought out that made us think of that possibility. Whether that would account for the tumor masses I do not know. I do not believe that we saw the films taken elsewhere, or if we did, I have forgotten.

DR. WYMAN: I am sorry we have not got them here to show you because, as I recall, the opinion of the X-ray Department was that the round masses described lay over the surface of the lung and along the parietal pleura. They were areas of round density, and we could not be sure that they were within the lung itself.

DR. KING: It sounds as if they were "consistent with the pleura."

#### CLINICAL DIAGNOSIS

Pleural endothelioma

DR. MILLER'S DIAGNOSIS

Sarcoma (of pleura or retropleural tissues)

#### ANATOMICAL DIAGNOSES

*Malignant teratoma of anterior mediastinum, involving pericardium, pleura and right lung*

*Hydrohemothorax, right.*

*Hydrohemothorax*

*Ascites*

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The operation mentioned at the termination of the history was a thoracoscopy. Examination of the aspirated fluid failed to show tumor cells, so that a thoracoscopy was done and a biopsy taken.

DR. JOHN G. SCANNELL: Two or three liters of bloody fluid was removed from the chest, and on inserting the thoracoscope one could see many raised, nodular, soft and purplish-blue areas on the parietal and visceral pleura. A biopsy was

taken. The lung could not be seen because there was so much bloody effusion, and the visceral pleura could not be identified.

DR. MALLORY: The biopsy specimen that Dr. Scannell provided us with showed a very undifferentiated tumor of relatively small cells, and we were finally persuaded to call it a mesothelioma. I know from long years of experience that that is a diagnosis one should never make and we were wrong once again. We have only 1 case in this hospital that I think may be a mesothelioma, and this is not it.

DR. KING: That is the one you burned me with once before.\*

DR. EDWARD D. CHURCHILL: Did the patient have x-ray treatment?

DR. MALLORY: Yes — quite a long course, with essentially no effect. He went steadily downhill and died three or four months after he was seen.

At autopsy we found an extensive tumor within the thoracic cage, both visceral and parietal pleuras on the right were solid masses of tumor, a large mass of tumor lay in the pericardial sac, another mass had invaded the right lung, destroying most of it beyond recognition, and still another mass of tumor was present in the anterior mediastinum. The tumor for the most part was quite soft and hemorrhagic and grossly was not characteristic of anything in particular. Microscopically, however, the diagnosis was immediately obvious. It showed a wide variety of types of tumor tissue, including squamous cells in some areas, gland formation in other places, large areas of endothelial-like tissue, which resemble closely the original biopsy, and in others, sarcoma, so that it was very evident that we were dealing with a teratoma. Teratomas are not uncommon in the chest, starting in the anterior mediastinum, and I think in all probability that was the primary source of this tumor.

\*Case Records of the Massachusetts General Hospital (Case 33111) *New Eng. J. Med.* 236:407-414, 1947.

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## THE ANNUAL MEETING

THE one hundred and sixty-seventh anniversary of the founding of the Massachusetts Medical Society will be observed at its annual meeting to be held at the Hotel Statler in Boston on May 25, 26 and 27, 1948. The attendance should exceed by a considerable number that of a year ago, when 1521 physicians registered. As has been the case since the program was expanded to occupy three entire days, the meetings of the supervising censors and of the Council will be held on the preceding day, May 24. The entire program is published elsewhere in this issue of the *Journal*.

The general scientific sessions, of which six have been arranged, will be held each morning and afternoon at 9 00 a.m. and 2 00 p.m. A variety of topics will be covered, including medical aspects of the atomic bomb, nuclear fission and its application to medicine, a symposium on diseases of the liver and government propaganda and socialized medicine.

After the annual meeting, to be held at 11 00 a.m. on Tuesday, May 25, the annual oration, "The Responsibility of Medicine in the Propagation of Poor Protoplasm," will be delivered by Dr. Allen S. Johnson, visiting physician to the Springfield Hospital. Following the precedent established last year by Dr. O'Hara, then president of the Society, the 18 members still in active practice who joined the society in 1898 will be presented at this meeting and will be the guests of the Society at the annual luncheon.

On the evening of May 25 the Shattuck Lecture, "Surgery in the Aged," will be delivered by Dr. C. Stuart Welch, professor of surgery at Tufts College Medical School and surgeon-in-chief of the Joseph H. Pratt Diagnostic Hospital and the Boston Dispensary. The seven scientific sections of the Society will hold their luncheon meetings at noon on May 26 and 27.

On Wednesday, May 26, after a preprandial course in the interests of social adjustment the members of the Society and their wives will assemble for the annual dinner at 7 00 p.m. The speaker of the evening will be Mary Ellen Chase, Ph.D., professor of English Language and Literature at Smith College. Her subject will be "The Country Doctor on the Maine Coast."

A special program has been prepared for the wives of fellows attending the meeting. On Tuesday, May 25, they will be taken on a bus tour through historic Cambridge, not neglecting the glass flowers, to equally historic Concord, and then on to Wayside Inn for lunch. A Pops concert has been arranged for that evening, and on the following afternoon a tea and fashion show will be given at Filene's.

The men's annual golf tournament is scheduled for the afternoon of Wednesday, May 26, at the Woodland Golf Club.

Not only are all fellows of the Society urged to attend the various sessions of the annual meeting they are urged also to visit the scientific exhibits, this year increased to fifteen in number, and the eighty-three technical exhibits, not the least of which are to be found in the balconies

### THE CUTTER LECTURE

It is often difficult to administer an endowed lectureship without modifying or losing altogether the original purposes that motivated the donor. Such loss of purpose is frequently glossed over by a statement of progress, which calls attention to the fact that times have changed, times do change but not so fast or as much as is generally implied by these subterfuges. It is therefore refreshing either to hear or to read a lecture like that of Dr Haven Emerson, published elsewhere in this issue of the *Journal*.

Here speaks a man whose career has led him down the middle of the road. Beside this road, throughout his lifetime, there have bloomed attractive wayside flowers with which he might have dallied, and there have been on either side inviting woodsy carpaths where he surely could have strayed and escaped from it all. If he had done so, however, he could not have written this lecture; he would have been a specialist in some subdivision of public health instead of its "general practitioner."

In addition to his qualifications to speak, this lecturer has expressed himself in graceful and at times lofty language. Just as he has effectively quoted Abraham Lincoln and Henry I. Bowditch, so too may future lecturers turn and glean from him incisive statements of our current views—our facts, freedoms and formulas, as well as our fears, frustrations and follies. Our present era may well be looked back upon as a period in which every "subway mole knows the news of good health often before his own physician has been convinced of its authenticity," or in which "daily bulletins come to the press from the hirelings of philanthropy instead of from responsible health officers."

In another vein the lecturer says "we could almost rest upon the record for a spell if some miracle of nice human relations brought us freedom from sneezes as the sanitary privy, clean water and pasteurized milk have spared us from most of the diarrheas and enteritides." Looking into the future "The very logic and economy of leaving the water of milk at the point of production and replacing it where the milk is consumed will force health departments to permit sale of reconstituted milk and to protect the consumer against its commercial abuse. The largest undertaking of the future, and perhaps the most important in the opinion of the lecturer, is the sanitation of occupations. The opportunity of health protection appears to me at least as promising in this area as in the two large fields of nutritional and communicable diseases." The sociologist also comes to the surface "There is no future of promise in any public service that permits or encourages a shift of responsibility for children from the home and the parents into schools and health agencies of government." The modern version of Matthew (5:45) appears in the discussion of today's poliomyelitis extravaganza when reference is made to 'the zooming airplanes that sprinkle death-dealing dust on house flies and honey bees alike.'

This Cutter Lecture contains much more that is quotable and thought-provoking; it is commended to our readers.

### WORLD HEALTH REPUDIATED

The failure of Congress to ratify the World Health Organization of the United Nations is reminiscent of its attitude in the last century toward the International Red Cross. At that time the United States and Russia, year after year, were the only major powers that turned thumbs down on one of the greatest humanitarian movements that the world has ever known.

The United States then was through with conflict. It had just fought a civil war and was never again going to resort to arms. It did not need the

Red Cross, nor was it going to become involved in entangling alliances

In the present instance the Senate has approved participation, and the House Foreign Affairs Committee has given its unanimous approval, it is the House Rules Committee that has tabled the legislation without an explanation

Two more ratifications were necessary to secure the twenty-six votes needed to make the World Health Organization a full-fledged agency of the United Nations. These have been obtained, but without the leadership of the United States the representation of the western hemisphere will scarcely count. A democracy can at least lead the world in blowing hot and cold with the same breath

## RED CROSS AND THE BLOOD BANKS

ATTENTION is directed to a letter published elsewhere in this issue of the *Journal* from Dr Lamar Soutter and Dr Charles P. Emerson, Jr, directors respectively of the blood banks of the Massachusetts General and the Massachusetts Memorial hospitals. If, as expressed in this communication, efforts are being made to interfere with the fullest development of the Red Cross blood-collection program, not only is the health of the public being put in jeopardy, but national security itself may be threatened

Any program may justly be subject to constructive criticism, the only serious opposition to this particular enterprise comes from organizations that may have cause to fear its competition. These consist largely of local hospital banks, and, as Dr Soutter and Dr Emerson state, the hospital banks that they direct have been helped rather than injured by the Massachusetts State bank that has been in existence for two years and will now turn over its functions to the Red Cross

It is an ambitious program for a time of peace on which the Red Cross has embarked. No one can guarantee or as yet predict its success. The Red Cross, nevertheless, is our accepted national agency

for relief in time of distress, local or widespread, and this blood program may logically be construed as falling within its legitimate field of activity. It is the obligation of every citizen, lay or medical, to support it to the limit of its needs

## MEDICOLEGAL ABSTRACT

**Regulation of Professional Conduct—Effect of acquittal in criminal case on board's suspension order** In Massachusetts the professions are regulated by one inclusive statute (G. L. [Ter. Ed.] C. 112), which provides for an administrative board empowered to revoke and cancel the certificate and registration of anyone found "guilty of deceit, malpractice, gross misconduct in the practice of his profession, or of any offense against the laws of the commonwealth relating thereto." In the event that a doctor is found "not guilty" by a jury in a criminal proceeding, or "not negligent" in a civil proceeding, is such a finding binding on the board that was not a party in the proceeding? If a doctor commits some offense other than one in the practice of his profession, is he liable to be suspended under the terms of the statute? A recent case involved both problems.

The Board of Dental Examiners revoked the certificate of a dentist and canceled his registration on the ground that in his application for registration he had falsely and with intent to deceive claimed to be a graduate of Montreal College of Dentistry. In a subsequent criminal proceeding under the criminal provisions of C. 112, s. 52, he was tried and acquitted by a jury of the charge of falsely and with intent to deceive claiming to be a graduate of a college granting degrees in dentistry. Fifteen years later he petitioned the Supreme Judicial Court for reversal of the revocation, and his petition was dismissed by a single justice since "for aught that appears there may have been ample evidence before the board in 1932 indicating that the diploma" presented by the petitioner was a forgery.

On appeal the decision was affirmed, for the court construed the term "any offense" to cover not only "misconduct as a dentist" but also "the violation of any law relating to the practice of the profession of dentistry" including laws "relating to admission to that profession." Of the acquittal the court said:

That fact, in our opinion, does not vitiate the action of the board, for one reason because that action preceded the acquittal in point of time. Furthermore, this is a civil proceeding, while the acquittal was in a criminal proceeding, and the parties to the two proceedings are different.

(*Giroux v. Board of Dental Examiners*, 76 N. E. [2d] 758, 1948)

## MASSACHUSETTS MEDICAL SOCIETY

## DEATH

LAMBERT — Frederick D. Lambert M.D. of Tyngsboro died on April 20. He was in his seventy-first year.

Dr. Lambert received his degree from Boston University School of Medicine in 1900 and from Harvard Medical School in 1901. He was a former president of Middlesex North District Medical Society and had been a member of the Council of the Massachusetts Medical Society since 1927.

His widow, four sons, two brothers and eight grandchildren survive.

MASSACHUSETTS DEPARTMENT  
OF PUBLIC HEALTHCOMMUNICABLE DISEASES IN  
MASSACHUSETTS FOR MARCH 1948

DISEASES	RÉSUMÉ		
	MARCH 1948	MARCH 1947	SEVEN YEAR MEDIAN
Chancroid	4	3	2*
Chicken pox	2405	3063	1604
Diphtheria	21	22	19
Dog bite	867	790	769
Dysentery bacillary	9	9	4
German measles	119	112	316
Gonorrhea	215	285	327
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	0	0*
Malaria	7	8	8
Measles	4205	1795	3126
Meningitis meningococcal	6	2	21
Meningitis, Pfeiffer-bacillus	2	4	4
Meningitis, pneumococcal	2	2	3†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	1	3†
Meningitis, other forms	1	0	0†
Meningitis undetermined	8	8	6†
Mumps	2522	1174	1549
Pneumonia lobar	145	172	369
Polioomyelitis	0	2	2
Salmonellosis	4	15	8
Scarlet fever	706	564	1457
Syphilis	226	364	462
Tuberculosis, pulmonary	241	167	148
Tuberculosis, other forms	29	14	20
Typhoid fever	1	3	2
Undulant fever	4	7	5
Whooping cough	241	645	553

\*Four year median.

†Six year median.

## COMMENT

Diseases with incidence above the seven-year median are chicken pox, diphtheria, bacillary dysentery, measles and mumps.

Diseases with incidence below the seven-year median are German measles, lobar pneumonia, salmonellosis, scarlet fever, typhoid fever, undulant fever and whooping cough.

Diphtheria is declining but the number of cases is still higher than in eight out of the ten previous years. Lobar pneumonia is at the lowest level ever reported. Scarlet fever is at the lowest prevalence, except for three years, since 1918, and whooping cough continues to make new low records.

Only twice in the past has the number of cases of chicken pox exceeded the number reported in March of this year. Measles is at the highest prevalence since 1943, and mumps at the highest since 1945.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston 11; Brockton, 1; Dedham 1; Duxbury 1; Malden 1; Medford 1; Quincy, 1; Revere 3; Somerville, 1; total 21.

Dysentery bacillary, was reported from Boston, 1; Marblehead 2; Melrose 1; Worcester, 5; total, 9.

Encephalitis, infectious was reported from: Lexington, 1; North Attleboro, 1; Somerville 1; Worcester 1, total, 4.

Malaria was reported from Amherst, 1; Ludlow, 1; Medford 3; Saugus, 1; Stoneham, 1; total 7.

Meningitis meningococcal was reported from Boston 2, Fitchburg, 1, Newton, 1; Pittsfield 1; Quincy, 1; total, 6.

Meningitis Pfeiffer bacillus, was reported from Amherst, 1; Everett, 1; total 2.

Meningitis, pneumococcal was reported from Holden, 1; Holyoke 1, total, 2.

Meningitis, streptococcal, was reported from Lowell, 1, total, 1.

Meningitis undetermined, was reported from Arlington, 1; Franklin, 1; Revere 1; Springfield 1; Templeton 2; Winchendon 1; Worcester 1; total 8.

Salmonellosis was reported from Auburn 1; Falmouth 1; Somerville, 1; Worcester 1; total 4.

Scarlet fever was reported from Boston 4; Everett, 1; total, 5.

Tetanus was reported from Cambridge 3; Danvers 2; Fall River 1; Medford 1; Somerville 1; total 8.

Typhoid fever was reported from Fall River 1; total, 1.

Undulant fever was reported from Acton 1; Bridgewater 1; Dudley, 1; Medway 1; total, 4.

LABORATORIES APPROVED FOR  
PREMARITAL AND PRENATAL  
BLOOD TESTS

The annual evaluation of the performance of laboratories doing diagnostic and serologic tests for syphilis has been completed. The laboratories now on the list approved for premarital and prenatal blood tests are as follows:

LOCATION	LABORATORY
Boston	Boston Dispensary
	Boston Health Department
	Commonwealth Clinical Laboratory
	Leary Laboratory
	Massachusetts General Hospital
	Massachusetts Memorial Hospitals (G. I. D. Clinic)
	State Wassermann Laboratory
	Brockton Health Department
	Sias Laboratory (Brooks Hospital)
	Clinton Hospital
Brockton	Union Hospital
	Barbank Hospital
	Fairview Hospital
	Holyoke Hospital
	Providence Hospital
Lowell	Lowell General Hospital
	Farren Memorial Hospital
	Clinical Laboratory
	St. Luke's Hospital
	Newton Wellesley Hospital
Newton	North Adams Hospital
	St. Luke's Hospital
	House of Mercy Hospital
	Salem Hospital
	Mersey Hospital
Springfield	State Infirmary and Hospital
	Noble Hospital
	St. Vincent Hospital
	Worcester City Hospital
	Worcester Health Department

## OFFICERS OF THE MASSACHUSETTS MEDICAL SOCIETY, 1947-1948



Bachrach

DR. DANIEL B REARDON, *President-Elect*

# PROGRAM OF THE ONE HUNDRED AND SIXTY-SEVENTH ANNIVERSARY OF THE MASSACHUSETTS MEDICAL SOCIETY

Monday, Tuesday, Wednesday and Thursday, May 24, 25, 26 and 27, Hotel Statler, Boston

The Registration Desk will be located on the Mezzanine Floor, and all who attend the meeting are requested to register

## MONDAY AFTERNOON MAY 24

- 4:00 Committee on Membership (PARLOR C)
- 4:30 Supervising Censors Meeting (PARLOR C)
- 6:00 Cotting Supper for Councilors (PARLORS A AND B)

9:30 *Treatment of the Anemias* DR. WILLIAM DAMESHEK, Boston Professor of clinical medicine, Tufts College Medical School hematologist, Joseph H Pratt Diagnostic Hospital

9:55 *The Relationship between the Industrial Physician and the Family Doctor* DR. THOMAS L. SHIPMAN, Manchester Instructor in industrial medicine, Harvard School of Public Health consultant in industrial medicine Salem Hospital clinical



Blackstone

DR. EDWARD P. BAGG, President



Art of Brown

DR. CHARLES J. KICKHAM, Past President

## MONDAY EVENING MAY 24

- 7:00 Annual Meeting of the Council (GEORGIAN ROOM)

## TUESDAY MORNING MAY 25

### First General Session

#### GEORGIAN ROOM

- DR. DWIGHT O'HARA Chairman
- DR. FREDERICK S. HOPKINS Co-chairman

- 9:05 A Motion Picture Entitled *Purposeful Splinting Following Injuries to the Hand* With a discussion by DR. SUMNER L. KOCH, MICHAEL L. VASON AND HARVEY S. ALLEN

assistant in medicine Massachusetts General Hospital

- 10:20 *Medical Aspects of the Atomic Bomb* DR. SNIELDS WARREN Boston Director division of biology and medicine, Atomic Energy Commission pathologist, New England Deaconess Hospital New England Baptist Hospital and Pondville State Hospital for Cancer

- 11:00 Annual Meeting of the Massachusetts Medical Society (GEORGIAN ROOM)

Annual Oration (following annual meeting) The Responsibility of Medicine in the Propagation of Poor Protoplasm DR. ALLEN S. JOHNSON Springfield Visiting physician Springfield Hospital



## THURSDAY AFTERNOON, MAY 27

## Sixth General Session

## GEORGIAN ROOM

DR. JOHN FALLON, *Chairman*DR. GEORGE S. REYNOLDS, *Co-chairman*

- 2 00 *Rubella and Congenital Defects* DR. CONRAD WESSELHOEFT, Boston Clinical professor of infectious diseases Harvard School of Public Health
- 2 25 *Endometriosis* DR. INGLIS F. FROST, New York City Chief of Endocrine Clinic, Women's Hospital
- 2 50 *Cutaneous Malignancies and Nevi* DR. EUGENE F. TRAUB, New York City Professor of dermatology, University of Vermont College of Medicine, formerly, clinical professor of dermatology and syphilology, New York Post-Graduate Hospital, Columbia University
- 3 15 *The Practical Importance of the Rh Factor* DR. LOUIS K. DIAMOND, Boston Assistant professor of pediatrics, Harvard Medical School, visiting physician, Children's Hospital, director, Blood Grouping Laboratory
- 3 40 *The Management of Surgical Pain* DR. EMERY A. ROVENSTINE, New York City Professor of anesthesia, New York University College of Medicine, director, Department of Anesthesiology, Bellevue Hospital
- 4 05 *Government Propaganda and Socialized Medicine* HON. FORREST A. HARNESS, member of Congress, Fifth District, Indiana
- 4 30 *Unexpected Death of Persons Not Suffering from Recognizable Disease* DR. ALAN R. MORITZ, Boston Professor of legal medicine, Harvard Medical School, pathologist-in-chief, Peter Bent Brigham Hospital

## SCIENTIFIC EXHIBITS

## BOOTH

- 81 — SPINDLE-CELL TUMORS OF THE GASTROINTESTINAL TRACT  
Sponsor Department of Roentgenology, Massachusetts General Hospital  
Exhibitors Dr. William L. Pallazzo and Dr. Milford S. Schulz  
METHODS OF REDUCTION AND FIXATION FOR FRACTURES OF THE JAW  
Sponsor Massachusetts General Hospital  
Exhibitor Dr. Kurt Thoma
- 82 — EPILEPSY ETIOLOGY AND TREATMENT  
Sponsor The Seizure Unit, The Children's Medical Center  
Exhibitors Dr. William G. Lennox and associates
- 83 — CORONARY HEART DISEASE  
Sponsor Departments of Medical Research and Pathology, Beth Israel Hospital  
Exhibitors Dr. Monroe J. Schlesinger, Dr. Herrman L. Blumgart and Dr. Paul M. Zoll  
PERITONEAL IRRIGATION FOR THE TREATMENT OF ACUTE RENAL FAILURE  
Sponsor The Surgical Department, Beth Israel Hospital

Exhibitors Dr. Howard A. Frank, Dr. Jacob Fine and Dr. Arnold M. Seligman

- 84 — PHOTOGRAPHIC EXHIBIT OF ACTIVITIES IN A FORMULA ROOM  
Sponsor Boston Lying-in Hospital
- 85 — VENOUS CATHETERIZATION OF THE HEART  
Sponsor Peter Bent Brigham Hospital  
Exhibitors Dr. Lewis Dexter and Dr. Merrill C. Sosman
- 86 — A DIRECT TEST FOR THE STUDY OF ASTHMA.  
Sponsor Allergy Clinic of the Evans Memorial and the Massachusetts Memorial Hospitals  
Exhibitors Dr. Francis C. Lowell and Dr. Irving W. Schiller
- 87 — DETECTION OF RADIOACTIVE MATERIAL.  
Sponsor Laboratory of Pathology and Radiation Department, New England Deaconess Hospital  
Exhibitors Russell F. Cowing and Charles K. Spalding  
PATHOLOGY OF RESECTED LUNGS  
Sponsor Laboratory of Pathology and Thoracic Service, New England Deaconess Hospital  
Exhibitors Dr. Richard H. Overholt and Dr. William A. Meissner
- 88 — POLYPS OF THE COLON AND RECTUM  
Sponsor Lahey Clinic  
Exhibitors Dr. Richard B. Cattell and Dr. Neil W. Swinton
- 89 — CARCINOMA IN SITU OF THE CERVIX AND ENDOMETRIUM  
Sponsor Free Hospital for Women  
Exhibitors Dr. Paul A. Younge and Dr. Arthur T. Hertig
- 90 — RHEUMATOID ARTHRITIS, ITS MEDICAL AND ORTHOPEDIC CARE.  
Sponsor Robert B. Brigham Hospital  
Exhibitors Dr. Theodore B. Bayles and Dr. Theodore A. Potter and associates
- 91 — REPAIR OF CLEFT LIPS  
Sponsor Plastic Division of the Department of Surgery, The Children's Hospital  
Exhibitor Dr. Donald W. MacCollum
- BALCONY
- 203 — HEART DISEASE IN THE PRODUCTIVE AGES — FOREMOST PUBLIC-HEALTH CHALLENGE  
Sponsor Massachusetts Heart Disease Study of the Massachusetts Department of Public Health, Harvard Medical School and the United States Public Health Service  
Exhibitors Dr. Vlado A. Getting, Dr. Lewis C. Robbins and Dr. Gilcin F. Meadors
- 206 — UROLOGICAL CASE STUDIES  
Sponsor Urological Department, Mount Auburn Hospital and Department of Surgery, Tufts College Medical School  
Exhibitors Dr. Harold A. Chamberlin and Dr. Joseph Fischmann

## TECHNICAL EXHIBITS

1948

Abbott Laboratories	
Alkalol Company	
Ames Company, Inc.	
Atlantic X-Ray Company	
Ayerst, McKenna & Harrison Ltd	
Baker Laboratories	
Chester A. Baker, Inc.	
Best Foods, Inc.	
Billhuber-Knoll Corporation	
The Borden Company	
Brewer & Company, Inc.	
Brown and Connolly, Inc.	
Buffington & Inc.	
Burrongs Wellcome & Company, Inc.	
Cambridge Instrument Company	
Camel Cigarettes	
Carnation Company	
Certified Milk Producers Association	
Ciba Pharmaceutical Products Inc.	
Coca-Cola Company	
Crosbie-Macdonald	
Davies, Rose & Company, Ltd	
F A Davis Company	
Denver Chemical Manufacturing Company	
Doho Chemical Corporation	
Dy Dee Service, Inc.	
Electro-Surgical Appliance Corporation	
J H Emerson Company	
C. B. Fleet Company	
General Electric X Ray Corporation	
Gerber Products Company	
J E. Hanger Inc.	
Hanovia Chemical & Manufacturing Company	
Harper X Ray Sales Company	
Harrower Laboratory Inc.	
Hoffmann-La Roche Inc.	
Kelly-Koett X Ray Company	
Kenmore Pharmacy Inc.	
H. W. Kinney & Sons Inc.	
George Laben	
Lederle Laboratories Division	
Ell Lilly and Company	
J B Lippincott Company	
M & R Dietetic Laboratories Inc.	
E. F. Mahady Company	
McIntosh Electric Corporation	
McNeil Laboratories Inc.	
Mead Johnson & Company	
Medical Clearing Bureau Inc.	
Medical Protective Company	
William S. Merrell Company	
National Dairy Products Company, Inc.	
National Drug Company	
T J Noonan Company	
E. L. Patch Company	
Parke, Davis & Company	
Pet Milk Company	
Philip Morris & Company, Ltd	
Picker X Ray Corporation	
Pitman-Moore Company	
Professional Equipment and Hospital Supply Co	
L. & B. Reiner	

Sanborn Company	8
Sandoz Chemical Works, Inc.	37
Saratoga Springs Authority	204
Schering Corporation	65
G D Searle & Company	71
Sharp & Dohme Inc.	50
Smith, Kline and French Laboratories	36
Spencer Inc.	62
E. R. Squibb & Sons	78
Surgeons and Physicians Supply Company	63
Swift & Company	32
Taibby-Nason Company	18
U S Vitamin Corporation	23
Vanta Company	62 A
Vaponefrin Company	66
Westinghouse Electric Corporation	67 & 68
White Laboratories Inc.	27 & 28
Winthrop-Stearns Inc.	53
Wyeth Inc.	64
F E. Young & Company	26

## ANNUAL GOLF TOURNAMENT

WOODLAND GOLF CLUB

NEWTON MASSACHUSETTS

WEDNESDAY AFTERNOON, MAY 26

1:00 p. m.

DR. HENRY W. GODFREY, Newton, Chairman

## MISCELLANY

## BRISTOL NORTH DISTRICT MEDICAL SOCIETY

At the annual meeting of the Bristol North District Medical Society held at the Taunton Inn on April 15 the need of communities being covered for medical emergencies was discussed. It was proposed that this problem be handled by individual cities and towns and that reports be presented at the next meeting.

The establishment of a district women's auxiliary was approved.

Mr. Charles J. Dunn discussed malpractice from the point of view of an attorney.

W. E. DAWSON Secretary

## MASSACHUSETTS TRUDEAU SOCIETY

At the annual meeting of the Massachusetts Trudeau Society held in Boston on April 14, the following officers were elected to serve for the term of one year: president, Dr. Donald S. King; vice-president, Dr. Theodore L. Badger, and secretary-treasurer Dr. Edward J. Welch.

## CORRESPONDENCE

## RED CROSS BLOOD COLLECTION PROGRAM

To the Editor: Recently many of us in the field of blood banking have been greatly concerned by the efforts of certain persons to sabotage the Red Cross blood collection program.

We believe that doctors everywhere should realize the importance of the Red Cross effort both locally and nationally. If it succeeds it will mean free blood available in large quantities when needed; it will mean free blood in small hospital areas where heretofore transfusions were often impossible; and last but not least, it will mean an adequate mechanism for blood collection and distribution in case of enemy attack.

There is a fear by some that their blood banks will be engulfed by the Red Cross. In Massachusetts we have had an

excellent state bank in operation for two years, recently taken over by the Red Cross. We have been greatly assisted by this bank, not engulfed by it. The Red Cross intends to maintain this bank's high standards, and has avowed that there will be no interference with established banks. The criticism has been made that the Red Cross program is a step toward socialized medicine. Do those who make this statement realize that, in case of war, if there is no voluntary organization of this sort to collect and distribute blood, the government will establish its own banking system? Lastly, certain persons have stated that the Red Cross program cannot succeed. We do not know whether it can or not, but we do know that it has made a good beginning and that the benefits to be derived in the care of patients make it worth while for all of us to give it our unqualified support. With that backing, its chances of being successful should be greatly enhanced.

LAMAR SOUTTER

Director of Blood Bank  
Massachusetts General Hospital

CHARLES P. EMERSON, JR.

Director of Blood Bank  
Massachusetts Memorial Hospitals

## MORE ON WHITE CROSS

Dr Channing Frothingham's letter, published in the *Journal* of May 6, was referred to Dr Elmer S. Bagnall, whose comments are as follows:

*To the Editor:* The first paragraph of Dr Frothingham's letter states that this is the first request from a representative of the Massachusetts Medical Society for information about White Cross. On the contrary, as president-elect of the Massachusetts Medical Society, I made identical suggestions at the Twentieth Century Club, on March 8, 1945, with Dr Allan M. Butler and Dr Nathaniel W. Faxon participating and the present Governor Bradford presiding.

The president of the Massachusetts Medical Society in 1939 was Dr Channing Frothingham. If, as the ex-officio chairman of the Public Relations Committee, he does not seem to recall now the sequence of facts, the records of that committee, which then handled all these matters for the Society, will substantiate my statements. I was secretary of the Public Relations Committee at that time.

I have known and liked Dr Frothingham since our days together at Camp Devens. I recall vividly how energetically we of the committee discussed the plans that were later known as the Blue Shield and the White Cross, as well as other proposals. I remember too that enabling legislation for both these plans was adopted almost simultaneously. So far as Dr Frothingham's attitude was concerned, I stand by the statement quoted from my article.

Subsequent discussion in the letter suggests that I had untruthful motives. Those of you who know me, know better. Perhaps I did not make it clear enough that such experimental plans as the White Cross could illuminate the path of those carrying responsibility for plans now operating so that they would not repeat misjudgments in purpose or timing. The Blue Shield carries on but needs to be constantly cautious in its evolution. As a director of Blue Cross I can say that more and better use of available information about rough roads by all concerned would have saved us recent unhappy experiences. It is unfortunate that there are too many people in this country who would welcome failure of the Blue Cross and Blue Shield plans.

Also, I want to state with proper emphasis that although the Massachusetts Medical Society did not endorse and adopt the White Cross as its own, the next president, Dr Walter Phippen, and the Society leaned backward not even to seem to be critical of it. The records of the Public Relations Committee will support this statement. I was still its secretary and well remember that some White Cross press reports seemed to want the public to believe the contrary.

Finally, if the White Cross plan was so well adapted to the needs of the people and met its demise only from the depletion of its ranks with war, I hope that now it will be resumed and contribute to everyone's objective — better medical care for more people.

ELMER S. BAGNALL, M.D.

281 Main Street  
Groveland, Massachusetts

## BOOK REVIEWS

*Aphasia: A guide of retraining.* By Captain Louis Granch, with an appendix in collaboration with Sergeant George W. Pangle. 8°, cloth, 108 pp. New York: Grune and Stratton, 1946. \$2.75.

During the war cerebral injury gave rise to a considerable number of patients who were handicapped by speech defects, particularly aphasia, but were otherwise in good health. The matter was given consideration by the United States Army Medical Corps as early as April, 1945, and a technical bulletin was issued. The author has had practical experience in training aphasic patients at one of the large hospitals established in this country. He based his work largely on the previous investigations of J. M. Nielsen and Kurt Goldstein. In his brief manual he gives the basic findings in cases of dysarthria, including aphasia, and outlines a method of rehabilitation that he has found successful. The book is of value particularly as it gives in some detail actual experiences in handling patients with this type of disability.

*Communal Sick-Care in the German Ghetto.* By Jacob R. Marcus, Ph.D., and Adolph S. Ochs, Professor of Jewish History, Hebrew Union College. 8°, cloth, 335 pp. Cincinnati: The Hebrew Union College Press, 1947. \$2.50.

The author presents a detailed study of Jewish communal care — the action of the Jewish community and its accredited agencies — in providing medical services in the German lands of the late medieval period. The region covered is roughly the Holy Roman Empire — primarily, Germany and the Hapsburg lands. However, frequent reference is made to Polish and even to English institutions, since the German or Ashkenazic rite was found or prevailed in these areas. No attempt has been made to investigate the Sephardic or Spanish-Jewish institutions in North Germany, Holland and England. The term "medieval" as used in this work refers to the period from about 1500 to 1800. The term "ghetto" is used in its broadest sense as a synonym for the Jewish quarter — the self-contained, legally recognized Jewish community of the sixteenth to the nineteenth century.

The work is divided into a number of chapters. The first discusses direct communal care of the sick. Then follow chapters on the origin, structure and operation of the *Hebra Kaddisha* (Holy Brotherhood), women's societies for the care of the sick, Jewish youth movements in Europe in the eighteenth century, the *Hekdesh* or Jewish hospital and the beginnings of the modern Jewish hospital. A number of appendixes contain reproductions of early documents and historical material supplemental to the text. A good index concludes the volume.

The material is well organized. The volume is a credit to the printers. The publishing is excellent. A good large type on soft, light paper makes reading a pleasure. This scholarly work should be in all history collections, medical and general.

*Office Treatment of the Eye.* By Elias Selinger, M.D. 8°, cloth, 542 pp., with 67 illustrations. Chicago: The Year-Book Publishers, Incorporated, 1947. \$7.75.

This well written volume contains 67 illustrations and 526 pages of text arranged in sixteen chapters, grouped under chemotherapy, foreign bodies, ocular injuries, refraction, ocular muscles, lacrimal apparatus, orbit, eyelids, conjunctiva, cornea, sclera, lens and vitreous, glaucoma, uveal tract, retina, optic nerve and appendix.

The author recognizes the wide latitude of opinion about the efficacy of therapy, and he draws upon 160 cited authorities, as well as his own clinical experience, to set down helpful suggestions for the reader. The book deserves a place on the shelf of the practitioner, whether he be a general practitioner or ophthalmologist, because it makes accessible the therapeutic measures of proved worth of yesterday, as well as the promising measures of today.

The work lends itself to minor criticism from the point of view of the ophthalmologist. Since more than half the procedures recommended by the author require hospitalization, the title of the book should omit the word "office," and thus be contracted to "Treatment of the Eye." The first and most prominent chapter is devoted to chemotherapy, which appears again and again in subsequent chap-

ters of the book. Although chemotherapy has its indications, it also has its contraindications and one must be wise in selecting the therapeutic agent in terms of greatest efficiency and least hazard. The author's statement in his preface, as well as his method of approach in the text itself implies that he is trying to steer a middle course—to serve the general practitioner and the ophthalmologist alike. To serve the former the text would have to teach anatomy, physiology, pathology, pharmacology and clinical diagnosis before considering therapeutics. The truth is that skill in diagnosis and treatment cannot be vicariously obtained but that it is the reward won by penetrating contacts with patients over the years.

*Dr Kirkbride and his Mental Hospital.* By Earl D. Bond M.D. 8 cloth 163 pp. with 7 illustrations. Philadelphia J. B. Lippincott Company 1947 \$3.50.

This book is a biography of Dr. Kirkbride and a history of the Pennsylvania Hospital for the Insane. The first part is devoted to the early life of the doctor, who was born in 1809 and died in 1883; his early education at Quaker schools, his medical years at the University of Pennsylvania, his years of early practice and his turn to psychiatry in 1840. The second part concerns the history of the hospital in its original building from 1841-1859 and in the second building finished in 1859. Dr. Kirkbride designed the second building after ideas original to him. At least thirty-one states built hospitals on his plan. He embodied his ideas and observations on the care of the insane in a book entitled *Hospitals for the Insane*, published in Philadelphia in 1854 and 1880 by the J. B. Lippincott Company. The doctor's life was filled with trials and tribulations because of his advanced ideas but he weathered all attacks. The hospital was never his chief concern; he was more interested in the patient as an individual. The biography is written in a easy, narrative style. It is well published and should be in all medical history collections.

*Diagnosis in Daily Practice. An office routine based on the incidence of various diseases.* By Benjamin V. White M.D. and Charles F. Geschickter M.D. 8 cloth 693 pp. with 360 illustrations and 104 tables. Philadelphia J. B. Lippincott Company, 1947 \$15.00.

An internist and a pathologist, happily teamed, have pooled their teaching experience to producing this well integrated work on diagnosis in daily practice. It is a good book—somewhat heavy in style but in several respects novel in approach and organization. The volume is extraordinarily compact even in the facing pages in the front and at the end are utilized. In the former there is a list of the major causes of death and disability in the United States prepared from the vital statistics of the Census Bureau and the National Health Survey so as "to bring them to the medical consciousness." In the latter there is a list of major abnormalities to be sought on routine examination together with supplementary procedures to be undertaken in the presence of routine findings and with references to the pages in which they are discussed.

The authors stress greatly what they term "presymptomatic medicine." It lies midway between preventive and therapeutic medicine, aimed at the recognition of abnormalities of structure or function which may be the basis of subsequent disability or disease and which may be only in incipient to the examination for a current illness or to a periodic health examination. Thus the physician examines the patient for a respiratory disease may discover some precancerous lesion of the skin. This phase of medicine has been made possible by newly acquired knowledge of the precursors or early stages of disease whose association with the fully developed forms was not previously recognized.

The book is richly illustrated by 360 unusually enlightening diagrams, tables and photographs in black and white and in color in a total of 700 pages. This is a notable pedagogic contribution. Many of the illustrations are credited to the Massachusetts General Hospital.

There are five parts: the diagnostic survey including a section on statistical methods; diagnosis of abnormal symptoms; diagnosis of abnormal physical findings; laboratory procedures and major diseases. The last part, which is exhaustive, considers diseases of the secretory organs of the

female reproductive organs and of the peripheral vascular and central nervous systems and the psychoses. There is even a section on the final one, on office arrangement and equipment, which the authors hold may influence the character of the physician's work.

On the whole this is a worth while reference work for the advanced student and the practitioner.

The increasing practice of printing important material on the lining papers of the binding of a volume cannot be too severely criticized. The papers become defaced and soiled from use and are lost in rebinding.

*The Practical Nurse.* By Dorothy Deming R.N. 8 cloth 370 pp. New York The Commonwealth Fund, 1947 \$3.00.

This is not a textbook of practical nursing but a comprehensive treatise on the need, usefulness and supervision of practical nurses in the home, in general and special hospitals, in industry and public health and in federal institutions. There are special chapters on training, supervision and legislation. To each chapter is appended a list of references for further reading. The appendixes include lists of textbooks and instruction outlines, approved schools of practical nursing (ten in Massachusetts, the second largest number in the country), and opinions concerning state licensure of practical nurses. The author believes that there is a need and future for the practical nurse but that there should be mandatory legislation to protect the public and the nursing profession. A definite long range plan is formulated for the training, utilization and protection of the practical nurse. The text is well written and the material well organized. The publication is excellent, well up to the high standard of the Commonwealth Fund. The volume is recommended for all medical and general libraries.

## BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Emotional Maturity. The development and dynamics of personality.* By Leo J. Saul M.A. M.D. associate professor of psychiatry, Temple University School of Medicine and special lecturer in psychiatric information, Bryn Mawr College. 8 cloth 338 pp. Philadelphia J. B. Lippincott Company 1947 \$5.00.

*Amiable Autocrat. A biography of Dr. Oliver Wendell Holmes.* By Eleanor M. Tilton Ph.D. 8 cloth 470 pp. New York Henry Schuman 1947 \$5.00.

*Medicine.* By A. E. Clark Kennedy M.D. F.R.C.P. physician to the London Hospital and dean of the medical school. Volume 1. *The patient and his disease.* 8 cloth 383 pp. Baltimore: Williams and Wilkins Company, 1947 \$6.00.

*Sexual Behavior in the Human Male.* By Alfred C. Kinsey, Sr. D. professor of zoology, Indiana University; Wardell B. Pomeroy, research associate, Indiana University; and Clyde E. Martin, research associate, Indiana University. 8 cloth 805 pp. with 173 illustrations and 162 tables. Philadelphia W. B. Saunders Company 1948 \$6.50.

*Psychopathology and Education of the Brain Injured Child.* By Alfred A. Strauss, psychoeducational consultant, Evanston, Illinois; and president, Cove Schools for Brain Injured Children, Racine, Wisconsin; and Laura E. Lehtinen, psychoeducational consultant, Evanston, Illinois; and educational director, Cove Schools for Brain Injured Children, Racine, Wisconsin. 8 cloth, 206 pp. with 46 illustrations. New York: Grune and Stratton, 1947 \$5.00.

## NOTICES

## ANNOUNCEMENTS

Dr J Dellinger Barney announces the removal of his office to 412 Beacon Street, Boston

Drs M Leopold Brodny and Daniel Rosen announce the removal of their offices to 636 Beacon Street, Boston, for the practice of urology

## HARVARD MEDICAL SCHOOL CLASS OF 1898

The fiftieth anniversary reunion and dinner of the Harvard Medical School Class of 1898 will be held at the Harvard Club of Boston, 374 Commonwealth Avenue, Boston, on Friday, June 11, at 7 00 p m

Members of the Class who intend to be present should notify the Harvard Medical Alumni Office, Harvard Medical School

## SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, May 18, at 12 m

Dr Wyland F Leadbetter will speak on the subject "The Diagnosis and Treatment of Infections of the Genitourinary Tract."

Physicians are cordially invited to attend

## BOSTON GASTROENTEROLOGICAL SOCIETY

A meeting of the Boston Gastroenterological Society will be held in the New Cheever Amphitheater, of the Boston City Hospital, Dowling Building, Boston, at 12 noon on Wednesday, May 19 Dr Frank H Lahcy will speak on the subject "Carcinoma of the Large Bowel, Ulcerative Colitis and Terminal Ileitis"

## MASSACHUSETTS PHYSICIANS' ART ASSOCIATION

An exhibition of works of art by members of the Massachusetts Physicians' Art Association will be held in Room 409, Hotel Statler, throughout the annual meeting of the Massachusetts Medical Society, May 25 to 27, from 9 a m to 5 p m

## NEW ENGLAND HEART ASSOCIATION

The annual Henry Jackson Lecture, under the auspices of the New England Heart Association, will be given by Dr André Cournand, associate professor of medicine, College of Physicians and Surgeons, Columbia University, in the Boston Medical Library, Boston, at 8 15 p m on Monday, May 24 His subject will be "Recent Developments in the Study of the Pulmonary Circulation in Chronic Pulmonary Diseases"

A short business meeting will precede the lecture Interested physicians and medical students are invited to attend

## ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The annual meeting of the Association of Military Surgeons of the United States will be held in San Antonio, Texas, from November 10 to 13, and not in Atlantic City, New Jersey, on May 4 and 5, as previously announced in the *Journal*

## AMERICAN COLLEGE OF RADIOLOGY

The annual meeting of the American College of Radiology will be held at the Sberaton Hotel, Chicago, on Sunday, June 20 A dinner in honor of former presidents of the College and a commemoration of the fiftieth anniversary of the discovery of radium will be features of the meeting

## RESIDENCIES IN PSYCHIATRY

Residencies in psychiatry are available at the Veterans Administration Hospital, Roanoke, Virginia Training will be given at the hospital under the supervision of the Department of Psychiatry, University of Virginia School of Medicine A three-year program approved by the American Medical Association will include didactic and clinical instruction in all phases of psychiatry and basic neurology Residents will also actively participate in methods and techniques of treating psychiatric patients

Applications should be addressed to the manager, Veterans Administration Hospital, Roanoke 17, Virginia

## POSITIONS OPEN IN VETERANS ADMINISTRATION HOSPITALS

The Chief Medical Director of the Veterans Administration has recently announced a new program regarding specialty practice in Veterans Administration hospitals The program will apply to graduates who have completed three years of formal training at other institutions and wish to complete the qualifications of their specialty boards through supervised practice in their chosen specialties as full-time Veterans Administration employees This program has already been approved by the boards in medicine, surgery and neuropsychiatry

The present plan, which has been made possible by the termination of the appointments of some 1400 to 1500 ASTP and V12 physicians by July 1, applies particularly to hospitals that are not located in cities where teaching institutions are now connected with the Veterans Administration All the supervising consultants, however, will be connected with medical schools

This program appears to offer an unusual opportunity for young men to demonstrate their ability and to gain unusual experience in a chosen field Application should be made to the nearest Veterans Administration Branch Office These are to be found in the following cities Boston, New York City, Philadelphia, Richmond, Atlanta, Columbus, Chicago, St Paul, St Louis, Dallas, Seattle, San Francisco and Denver

## MEDICAL AND SURGICAL SUPPLIES FOR PALESTINE

Because of the extreme need for medical and surgical supplies for the care of wounded Jews in Palestine, the Greater Boston Medical Society is sponsoring a drive for the following articles surgical instruments of all types penicillin, streptomycin, syringes of all sizes, needles of all sizes, bandages, and gauze pads Cash contributions for the purchase of such supplies will also be welcomed, checks should be made payable to the Greater Boston Medical Society and mailed to Dr Bernard I Goldberg, 481 Beacon Street, Boston Any supplies contributed should be delivered to Dr Goldberg, to Dr David Davis, 416 Marlborough Street, Boston, or to the Brookline Hadassah Office, 251 Harvard Street (Room 7), Brookline

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 20

THURSDAY, MAY 20

12 00 m Clinical Staff Meeting Nurses' Home, Allerton Hospital, Brookline

FRIDAY, MAY 21

\*9 00-10 00 a m Problems Relating to Bacterial Resistance. Dr Tom Fite Paine, Jr Joseph H Pratt Diagnostic Hospital  
\*10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital

MONDAY, MAY 24

\*12 00 m Clinicopathological Conference. Margaret Jewett Hall Mt. Auburn Hospital, Cambridge  
\*8 15 p m New England Heart Association Boston Medical Library

(Notices concluded on page xvii)

NOTICES (Concluded from page 722)

TUESDAY MAY 25

- \*12:15-1:15 p.m. Clinico-radiogenetic Conference Peter Bent Brigham Hospital.
- \*1:30-2:30 p.m. Pediatric Rounds Burnham Memorial Hospital for Children Massachusetts General Hospital

WEDNESDAY MAY 26

- \*9:00-10:00 a.m. Non-Specific Urethritis. Dr. Lewis W. Kane Joseph H. Pratt Diagnostic Hospital
- \*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital.) Amphitheater Peter Bent Brigham Hospital
- \*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater Children's Hospital.

\*Open to the medical profession

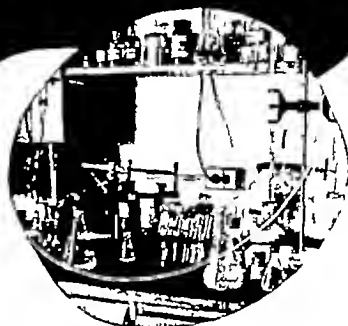
- MAY 16-22. American Board of Obstetrics and Gynecology Inc Page 344 issue of March 4
- MAY 16-23 International College of Surgeons. Page 136, issue of January 22.
- MAY 17-19 American Ophthalmological Society Page 422 issue of April 1
- MAY 17-20. American Urological Association Hotel Statler Boston
- MAY 17-20. Association for the Study of Internal Secretions. Page 492 issue of April 1
- MAY 17-20. American Psychiatric Association Page 614 issue of April 22.
- MAY 18. South End Medical Club Page 722
- MAY 18-22 American Association on Mental Deficiency Copley Plaza Hotel, Boston
- MAY 19 Boston Gastroenterological Society Page 722
- MAY 20. Massachusetts Tuberculosis League Inc. Page 647 issue of April 29
- MAY 20-25 American Board of Ophthalmology Page 170 issue of January 29
- MAY 23-28 American Physiotherapy Association Page 543 issue of April 8.
- MAY 24 New England Heart Association Page 722
- MAY 24-26. American Gynecological Society Page 543 issue of April 8
- MAY 24-27 Massachusetts Medical Society Annual Meeting Hotel Statler Boston
- MAY 25-27 Massachusetts Physicians Art Association Page 722
- MAY 26. Massachusetts Medical-Legal Society Page 678 issue of May 6
- MAY 27-29 American Radiological Association Page 455 issue of March 25
- JUNE 2. Children's Hospital Alumni Association Page 648 issue of March 25
- JUNE 3-6. American Orthopaedic Association Page 614 issue of May 6
- JUNE 7-10. National Gastroenterological Association Page 455 issue of March 25
- JUNE 11 Harvard Medical School Class of 1898 Page 722
- JUNE 14-16. American Neurological Association Page 582, issue of April 15
- JUNE 17-20. American College of Chest Physicians Page 455 issue of March 25
- JUNE 20 American College of Radiology Page 722
- JUNE 20 and 21 American Radium Society Page 543 issue of April 8.
- JUNE 21 and 22. American Society for the Study of Sterility Page 384 issue of March 11
- JUNE 23. University of Pennsylvania Medical Alumni Society Page 678, issue of May 6
- JUNE 25 and 26. Christian Medical Society Page 492 issue of April 1
- JUNE 28-30. American Academy of Pediatrics. Hotel Schroeder Milwaukee Wisconsin
- JULY 6-24 Students International Clinical Congress Page 455 issue of March 25
- JULY 12-17 First International Polio-myelitis Conference. Page 36, issue of January 1
- AUGUST 11-21 International Congress on Mental Health. Page 344 issue of March 4
- AUGUST 23-26. International Society of Hematology Page 419 issue of March 18
- AUGUST 26-28 American Association of Blood Banks. Page 420 issue of March 18.
- SEPTEMBER 7-11 American Congress of Physical Medicine. Page 582, issue of April 15
- SEPTEMBER 13-15 American Academy of Pediatrics. Olympic Hotel Seattle Washington
- SEPTEMBER 20-23 American Hospital Association Page 310 issue of February 26
- SEPTEMBER 29 Mississippi Valley Medical Editors Association Page 170 issue of January 29
- OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29
- NOVEMBER 1-3 American Clinical and Climatological Association Page 582, issue of April 15
- NOVEMBER 8-12. American Public Health Association Page 420, issue of March 18
- NOVEMBER 10-13 Association of Military Surgeons of the United States. Page 722
- NOVEMBER 20-23 American Academy of Pediatrics. Annual Meeting California Madison Hall Hotel Atlantic City New Jersey
- DECEMBER 7-9 Southern Radiological Association Annual Meeting Page 313 issue of April 8.

DISTRICT MEDICAL SOCIETY

PLYMOUTH

MAY 20. Lakeville Sanatorium Lakeville

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Number 21

## PORTACAVAL SHUNTS IN THE TREATMENT OF PORTAL HYPERTENSION\*

With Special Reference to Patients Previously Operated Upon

ROBERT R. LINTON, MD†

BOSTON

A NEW chapter is being written on the treatment of portal hypertension with bleeding esophageal varices. Eck,<sup>1</sup> in 1877, was the first to demonstrate that the portal vein can be anastomosed to the inferior vena cava in animal experiments. From then until 1945 only a few sporadic attempts of portacaval shunts in human beings were reported in the literature. Most of these were unsuccessful, but with the recent favorable reports of Whipple<sup>2</sup> in 1945 and Blakemore<sup>3</sup> in 1945 and 1947, a renewed interest has been stimulated in this subject. These authors have described two types of venous shunts to reduce the portal hypertension: an end-to-end anastomosis between the splenic and left renal veins, after a splenectomy and a left nephrectomy have been performed, and an end-to-side anastomosis between the distal end of the divided portal vein and the inferior vena cava. As a result of accumulated experience in this new surgical field it has been found that it is not possible to utilize either type of venous anastomosis in every case. This is especially true in cases in which a previous splenectomy has been done in an attempt to control the portal hypertension and bleeding from the esophagogastrintestinal tract. Furthermore, it has seemed undesirable to remove a healthy organ, such as the left kidney, unless it is otherwise impossible to make a satisfactory shunt. Accordingly, an end-to-side anastomosis between the end of the splenic vein and the side of the renal vein without nephrectomy has been developed.<sup>4</sup>

The purpose of this paper is to report 4 cases of portal hypertension secondary to an extrahepatic portal bed block with continued esophagogastrintestinal bleeding despite previous surgical procedures. Three patients had had splenectomies, and the other multiple operations in an attempt to control the portal hypertension.

### CASE REPORTS

**CASE 1.** L. M. (M.G.H. 21,099), a 12-year-old boy, was admitted to the hospital on December 17, 1929, because of hematemesis. He had been admitted to the Children's Hospital, Boston, in 1925 and 1927 because of similar episodes. In that institution the bleeding had stopped spontaneously after a transfusion. The most recent episode of bleeding had begun 2 days before admission.

Physical examination revealed an enlarged spleen. A diagnosis of bleeding esophageal varices due to splenic vein obstruction (Banti's syndrome) was made. After appropriate preoperative care, a splenectomy by an abdominal approach was performed by Dr. Arthur W. Allen. The patient did well and was discharged on January 25, 1930.

He was readmitted on November 11, because of hematemesis. Operation was performed by Dr. Allen, who ligated numerous dilated veins in the gastrohepatic omentum and in the region of the left gastric vein. The patient was discharged on December 24 and was subsequently readmitted on January 15, 1931, for a tonsillectomy on April 23, 1932, because of hematemesis, on February 14, 1937, because of hematemesis and on January 15, 1944, because of hematemesis and for an esophagoscopy and injection of the varices with 5 per cent sodium morrhuate solution. Between January 8 and July 13, 1945, the patient was readmitted five times for esophagoscopy and injection of varices. He was well until September 22, when he vomited about 500 cc. of blood. He was readmitted for a portacaval anastomosis.

At operation on October 9, the superior mesenteric vein was isolated at the base of the mesentery of the small bowel. It was divided and the proximal end was anastomosed to the side of the inferior vena cava distal to the renal veins (Fig. 1). Biopsy showed a normal liver. The patient made a satisfactory recovery and was discharged from the hospital 15 days after the operation.

When seen on August 8, 1947, he had had no further esophagogastrintestinal bleeding and was working full time as a painter. A gastrointestinal series revealed no change in the esophageal varices. The hemoglobin was 13.9 gm. per 100 cc. and the white-cell count 9700.

**CASE 2.** F. L. (M.G.H. 333,628), a 16-year-old schoolgirl, was admitted to the hospital on December 25, 1941, because of a sudden hematemesis of 1 day's duration. Physical examination revealed an enlarged spleen two fingerbreadths below the costal margin. A roentgenogram of the esophagus showed large esophageal varices. Liver function tests were negative. A diagnosis of splenomegaly with esophageal varices (Banti's syndrome) was made. On January 19, 1942, a splenectomy and ligation of several large periesophageal varices were done through a transthoracic approach by Dr. Richard H. Sweet. The patient was discharged from the hospital on February 28.

She was seen occasionally in the Out Patient Department and Medical Clinic and was well without symptoms until April 11, 1946, when she was readmitted to the hospital because of hematemesis of 1 day's duration. She was dis-

\*Presented at the annual meeting of the New England Surgical Society, Providence, Rhode Island, October 3, 1947.

†From the Department of Surgery, Massachusetts General Hospital, Associate in surgery, Harvard Medical School, visiting surgeon and chief, Peripheral Vascular Clinic, Massachusetts General Hospital.



charged on May 3. The patient re-entered the hospital for a portacaval shunt on July 5. An operation on July 13 was performed through a transabdominal left subcostal incision. It was impossible to find the splenic vein, since its proximal end had become fibrosed and narrowed, and it was un-

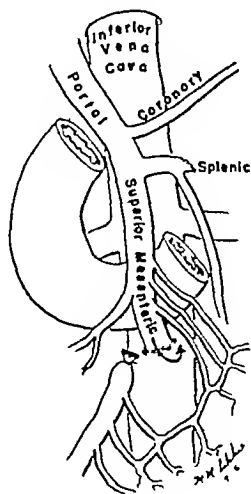


FIGURE 1 Schematic Drawing, Showing the Anastomosis between the Proximal End of the Divided Superior Mesenteric Vein and the Side of the Inferior Vena Cava Distal to the Renal Veins

This type of shunt was used in Case 1, and since it was performed the patient has had no further esophagogastrintestinal bleeding for over twenty-two months

suitable for a venous anastomosis. The largest vein in the portal system that could be found was the inferior mesenteric vein, which was divided and the proximal end anastomosed to the left ovarian vein (Fig 2). The liver biopsy was

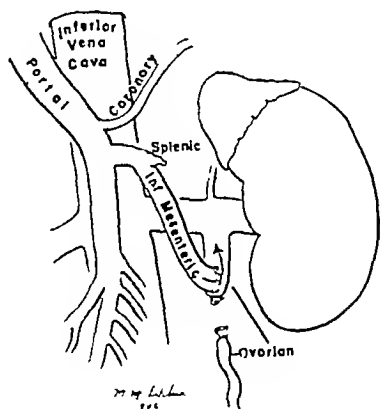


FIGURE 2 Schematic Drawing, Showing the Anastomosis between the Proximal End of the Divided Inferior Mesenteric Vein and the Side of the Left Ovarian Vein

It was necessary to sever the ovarian vein because of tension on the anastomosis. This type of shunt was used in Case 2, and since it was performed the patient has had no further esophagogastrintestinal bleeding for over fourteen months

reported as normal. The patient did well and was discharged from the hospital on July 30.

The patient has been seen several times in the Out Patient Department and she has had no symptoms. A repeat gastrointestinal series in June, 1947, revealed the esophageal varices to be unchanged. However, she has had no further bleeding in the 14 months since the operation.

CASE 3 J M (MGH 36), a 19-year-old male dental mechanic, was admitted to the hospital on November 6, 1935, because of tarry stools of 1 day's duration. Physical examination revealed that the liver and spleen were both slightly enlarged. A gastrointestinal x-ray series revealed extensive, large esophageal varices. A diagnosis of Banti's disease with bleeding esophageal varices was made. On December 5 the splenic artery was ligated in continuity with chromic catgut by Dr Beth Vincent, and an extensive intraperitoneal omentopexy was performed at the same operation. The patient did well and was discharged on December 20.

On January 2, 1937, he was readmitted because of hematemesis and tarry stools of 1 day's duration. He had repeated massive hematemeses on January 18, 19 and 20, requiring eight transfusions. He steadily improved, and a second operation was performed on February 3 by Dr Arthur W. Allen. Several large veins on the diaphragm along the lesser curvature of the stomach were ligated. The patient was discharged on March 2. He was readmitted on February 14, 1939, because of repeated tarry stools, and was discharged on March 17. He was subsequently admitted on April 28 and August 21, 1939, and February 7 and August 16, 1940,

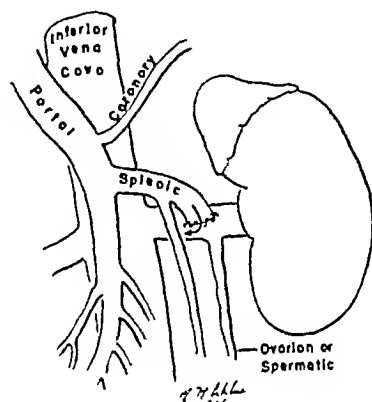


FIGURE 3 Schematic Drawing, Showing the End-to-Side Splenorenal Anastomosis, with Preservation of the Left Kidney. This is the operation of choice in cases especially with a cavernomatous transformation of the portal vein, since a direct portacaval anastomosis cannot be performed in such patients. It should be performed at the same operative procedure as the splenectomy. This type of shunt was used in Case 3, and since it was performed the patient has had no further esophagogastrintestinal bleeding for over fourteen months.

because of melena. On October 31, 1940, he re-entered the hospital for esophagoscopy, being discharged on November 6. Because of melena he was again admitted on November 7, five esophagoscopies, with injection of varices, were performed, and he was discharged on December 23. Between re-entry on January 9 and discharge on February 6, 1941, four esophagoscopies, with injections, were performed. Another episode of melena caused him to be readmitted on February 13, esophagoscopy, with injection of varices, was performed, and he was discharged on March 13. He re-entered the hospital on April 14 because of melena, esophagoscopy was performed, and he was discharged on May 2. Between May 18 and November 14 he was admitted seven times for esophagoscopy and injection of esophageal varices. At the twentieth admission, on February 5, 1942, cannulation of an intercostal vein for phlebography was attempted, the patient being discharged the next day. Between June 17 and June 26 he was readmitted because of melena. On July 25 he re-entered the hospital for a transthoracic exposure of the esophagus and ligation of several large periesophageal veins, performed by Dr Richard H. Sweet, and was discharged on August 12. He was readmitted for 2 days on September 11 for esophagoscopy and for 9 days on November 5 because of melena. Between April 4 and May 13, 1943, he was readmitted because of hematemesis and melena. On June 14, 1943, March 17 and October 27, 1944, and March 3 and September 21, 1945, he re-entered the hospital

for esophagoscopy and injection of esophageal varices each admission lasting 2 days. He was readmitted on March 28, 1946, because of hematemesis, and esophagoscopy and injection of esophageal varices were performed, the patient being discharged on March 30. On April 6 he was hospitalized because of massive hematemesis of 1 day's duration. At operation on April 24 through a right abdominal incision the portal vein could not be exposed because of the extensive hemorrhage. In the dissection the common bile duct was accidentally transected, and the cystic duct was also injured. Accordingly, a cholecystectomy and a choledochojunostomy were performed the latter according to Allen's method. The patient made a slow but satisfactory recovery, being discharged on May 29. On June 6 he was readmitted for a final attempt at a portacaval shunt. At operation on June 8 the spleen was exposed through a left thoracoabdominal incision. It was removed with great difficulty owing to numerous vascular adhesions including many formed as a result of the omentopexies. Considerable blood was lost and the patient received 3000 cc. of citrated blood by transfusion from the blood bank and at least 3000 cc. of citrated blood by autotransfusion. An end-to-side suture anastomosis was accomplished between the splenic vein and the renal vein after the removal of the spleen (Fig. 3).<sup>\*</sup> The renal artery was occluded for 20 minutes during the construction of the anastomosis. The operation required 6½ hours and the patient was under anesthesia for 7 hours and 45 minutes. Oliguria developed on the day after operation persisting for several days. The blood nonprotein nitrogen gradually rose to 103 mg per 100 cc. on the 6th postoperative day and then gradually returned to normal. At discharge from the hospital on May 29 it was 18 mg per 100 cc., and the urine concentrated to 1,003.

The patient was last seen on August 8, 1947 when he felt well and had had no further bleeding episodes after the splenorenal anastomosis had been completed. The hemoglobin was 17 gm per 100 cc. and the white-cell count 10,000, the urine concentrated to a specific gravity of 1.022. The nonprotein nitrogen was 27 mg per 100 cc. The esophageal varices, however, appeared unchanged on x-ray examination.

**CASE 4.** M. M. (M.G.H. 434-339) a 19-year-old girl was admitted to the hospital on February 4, 1944, because of repeated episodes of hematemesis over a 5-year period. The last attack had begun 5 days before admission.

Physical examination revealed a large young woman in no acute distress. The abdomen was normal except that the spleen could be palpated three fingerbreadths below the costal margin. The liver was not enlarged. A roentgenologic examination of the gastrointestinal tract showed esophageal varices. A liver biopsy specimen obtained by percutaneous biopsy was reported as showing a normal liver. A diagnosis of Bant's syndrome was made. On March 9 a splenectomy was performed through a transthoracic approach by Dr. Richard H. Sweet. The splenic vein was noted to be about 2 cm in diameter. In addition several large periesophageal veins and the left gastric vessels were ligated. The patient was discharged on April 3.

She was readmitted on December 12 because of hematemesis. She recovered from the hematemesis rapidly but the hospital stay was greatly prolonged because of the onset of vague abdominal discomfort and fever. A diagnosis of probable thrombophlebitis in the portal venous system was made. On June 25, 1945, an attempt was made to perform a portacaval anastomosis but this was found to be technically impossible because of cavernomatous transformation of the portal vein. The patient was discharged on July 11. She was hospitalized in another city during September because of hematemesis. On December 11, 1946 she was readmitted for a second attempt at a portacaval anastomosis, which proved to be technically impossible and was discharged on January 26, 1947. She was again admitted on February 28 because of hematemesis, being discharged on February 28 and on March 4 for another attempt at a portacaval anastomosis. At operation on March 10 the left upper quadrant of the abdomen was explored through a thoracoabdominal incision. An extensive search was made for the stump of the splenic vein which could not be found despite the fact that at the time of the splenectomy it had measured about 2 cm in diameter. Finally an anastomosis

was accomplished between the proximal end of a large branch of the inferior mesenteric vein to the side of the left adrenal vein. The patient made a satisfactory convalescence but it was believed that decompression of the pressure in the portal vein was not satisfactory because of the small diameter of the veins used in the venous shunt. She was discharged 10 days later. She re-entered the hospital because of hematemesis on July 25, being discharged on August 13, and on August 15, being discharged on September 9.

On September 17 she was readmitted for a final attempt to produce a portacaval shunt. At operation on September 20 the abdomen was opened through a long right subcostal incision. Another attempt to isolate the portal vein was fruitless owing to the vascularity of the region and also a porky type of induration in the region of the gastrophrenic ligament. A further search was made for other venous channels to anastomose to the inferior vena cava, but none were found that would have been suitable. The patient made a satisfactory recovery, but remains in the hospital because of further esophagogastrintestinal bleeding.

## DISCUSSION

The construction of blood-vessel anastomoses to shunt the blood flow from one part of the body to another has been perfected in recent years through the stimulus of the work of Whipple,<sup>2</sup> Blakemore<sup>4</sup> and Blalock.<sup>7</sup> The results obtained with portacaval shunts in patients with extrahepatic portal bed block (Bant's syndrome) have been extremely encouraging. In 7 cases in which a satisfactory shunt has been performed, to be reported elsewhere, no patient has bled over periods of two to twenty-two months, although roentgenologic examinations of the esophagus still show the presence of varices. The case reports presented above serve to demonstrate certain points that need emphasis in this new form of treatment. All 4 patients had had previous operations in an attempt to relieve the portal hypertension and bleeding from the esophagogastrintestinal tract, but no operation had been successful. Splenectomy had been performed in 3 cases, and in Case 3, although numerous surgical procedures had been done through both the abdomen and the chest, the spleen had not been removed.

Case 1 had a total of fourteen hospital admissions over a twenty-year period from the onset of the illness. The surgical procedures performed included splenectomy, ligation of the left gastric vein and the periesophageal veins transabdominally, five esophagoscopies, with injection of the esophageal varices with a sclerosing solution. Despite these varied forms of surgical treatment, the patient continued to bleed at intervals. The longest period of respite was from 1932 to 1937. It seems apparent, however, that none of the procedures had much effect on the portal hypertension, since at exploration in October, 1945, the pressure in the portal vein was equivalent to 47 cm. of physiologic saline solution — over four times the normal level. This case is also of interest because of the fact that the previous splenectomy precluded the production of a splenorenal anastomosis and that, owing to a cavernomatous transformation of the portal vein that made it impossible to isolate this vessel, a portacaval anastomosis could not be performed. Instead, the superior mesenteric

<sup>\*</sup>The technique of this operation has been described elsewhere.<sup>8</sup>

vein was isolated at the base of the mesentery and transected, and the proximal end anastomosed to the inferior vena cava just distal to the renal veins. This type of shunt functions because there are no valves in the portal venous system, so that blood can flow in a reverse direction into the inferior vena cava. There are sufficient collateral venous channels around the base of the mesentery to permit blood from the intestines to enter the portal system proximal to the point at which the superior mesenteric vein is interrupted and thus to gain entrance to the venous shunt. The result of this type of

Whether the venous shunt that was constructed — namely, the inferior mesenteric to the left ovarian vein — will produce a satisfactory reduction in the portal hypertension for a long time, it is difficult to say. It is encouraging, however, that the patient had had no further bleeding fourteen months after operation. If further hemorrhage develops it is planned to explore the right side of the abdomen to determine if it is possible to anastomose the portal vein to the inferior vena cava, or possibly the superior mesenteric vein to the inferior vena cava.

In Case 3 eighteen of the thirty-three hospital admissions were for massive bleeding, twelve for melena, and six for hematemesis. During this period the patient had many other bleeding episodes for which he was not hospitalized. This case demonstrates the apparent effectiveness of splenectomy and an end-to-side splenorenal shunt in the control of esophagogastrintestinal bleeding from portal hypertension and the failure of other methods of surgical treatment, which included ligation of the splenic artery and an omentopexy, ligation of the left gastric and coronary veins and an omentopexy, transthoracic ligation of the periesophageal veins and multiple esophagoscopies, with injections of the esophageal varices with a sclerosing solution. The hazard of attempting a portacaval anastomosis, in the presence of the cavernomatous transformation of the portal vein, is also obvious. The common bile duct and the cystic duct were damaged, so that it was necessary to perform a cholecystectomy and a choledochojejunostomy to save the patient's life. Fortunately, he withstood this procedure, and later it was possible to do a splenectomy and an end-to-side splenorenal anastomosis. The successful outcome of the shunt operation is believed to have been due to a number of factors, chiefly, to the utilization of the thoracoabdominal approach, multiple blood-bank transfusions and autotransfusions and the preservation of the left kidney. The importance of preserving the left kidney in this type of surgical procedure cannot be too strongly emphasized, since even with both kidneys this patient developed oliguria for several days and the nonprotein nitrogen level rose to over 100 mg per 100 cc after the splenorenal shunt. It seems very likely that he would have succumbed to uremia if a nephrectomy had been performed. It is still too early to speak of a cure, but at least the patient has had a period of over fourteen months without bleeding, which is the longest respite that he has had since 1937.

In summary, the patient was hospitalized for a total of five hundred and two days because of the portal hypertension. This was 13 per cent of the total time elapsed from the onset of the illness to the last discharge from the hospital. While in the hospital he had five major surgical operations, sixteen esophagoscopies, with injections of sclerosing solution, and a total of sixty-two blood transfusions (Fig 4).

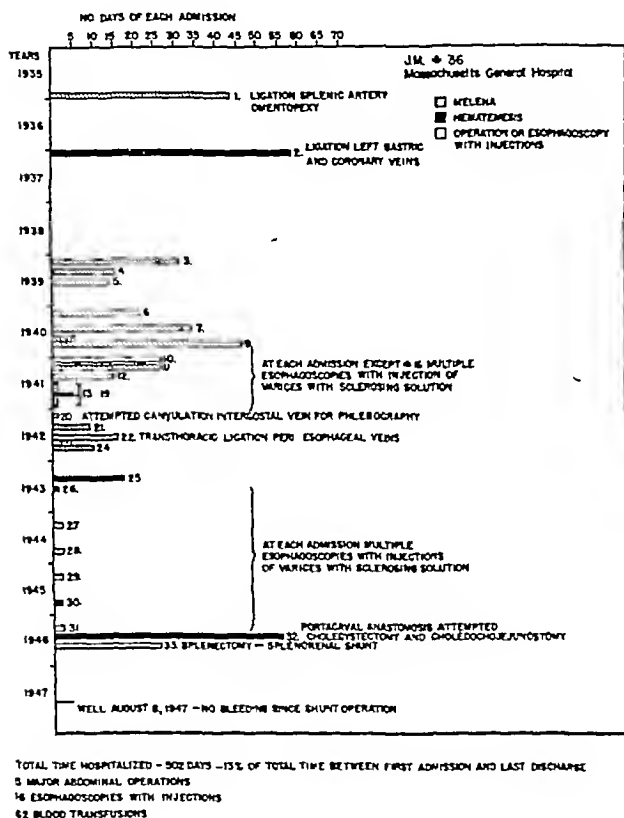


FIGURE 4 Number and Duration of Hospital Admissions for Esophagogastrintestinal Hemorrhages and Therapy in Case 3 and Surgical Procedures Performed

portacaval shunt in this case is encouraging, since there has been no evidence of bleeding over a period of twenty-two months since operation. Another case, with an anastomosis of the superior mesenteric vein to the inferior vena cava, was reported by Bogoraz<sup>8</sup> in 1913, but with a follow-up study of only one month, according to Whipple.<sup>2</sup>

In Case 2 the patient had three hospital admissions. This case also demonstrates the ineffectiveness of a splenectomy and ligation of the periesophageal varices through a transthoracic approach in the treatment of portal hypertension over a prolonged period, although a respite was apparently obtained for a period of about four years. It also demonstrates the impossibility of performing a splenorenal shunt once the spleen has been removed.

Case 4, in which there were eight hospital admissions over a period of three and a half years, also demonstrates the failure of splenectomy and the ligation of the periesophageal varices to control esophagogastrintestinal bleeding, since the patient was readmitted to the hospital because of recurrent hematemesis only eight months after this operation. The case illustrates, in addition, that after a previous splenectomy it may be impossible to perform a satisfactory portacaval shunt of any type. When the spleen was removed the splenic vein was noted to be about 2 cm. in diameter, an excellent vessel with which to do a splenorenal anastomosis. At four subsequent operations it was impossible to find a suitable vessel for a satisfactory shunt. The splenic vein, which had been so large originally, had shrunk down and was replaced by innumerable smaller vessels, none of which were suitable to use. It should be pointed out that at the time the splenectomy was performed in this patient and in 2 of the others the operation of portacaval anastomosis was not a generally accepted surgical procedure. The prognosis is extremely grave, since undoubtedly the patient will continue to bleed and will ultimately succumb from hemorrhage. *In the face of these facts and the good results to date with splenorenal shunts, it seems apparent that a surgeon who does a splenectomy for portal hypertension (Banti's syndrome) should perform a splenorenal anastomosis at the same operation, since this may be the only opportunity for the anastomosis.*

#### SUMMARY

Four cases are presented in 3 of which the results obtained in the treatment of portal hypertension, secondary to an extrahepatic-bed block (Banti's syndrome), by the formation of portacaval shunts were encouraging, since none of the patients with satisfactory shunts has bled since they were performed.

The most satisfactory portacaval shunt seems to be an end-to-side suture type of splenorenal anastomosis performed at the same operation at which the spleen is removed.

In some patients who have had previous splenectomies it may be possible to perform other types of portacaval shunts, such as a superior mesenteric vein to inferior vena cava or inferior mesenteric vein to left ovarian vein. Two patients have gone twenty-two and fourteen months since the shunts were performed without evidence of esophagogastrintestinal hemorrhages.

A direct portacaval anastomosis was not possible in 3 of these cases because of a cavernomatous transformation of the portal veins.

It is believed that a surgeon should not do a splenectomy in a case of portal hypertension unless he is prepared to do a splenorenal anastomosis at the same operation, since this may be the only opportunity to construct a satisfactory shunt.

A longer period of observation is necessary to determine whether the portal hypertension and the tendency to esophagogastrintestinal hemorrhages have been permanently affected.

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# SALMONELLA OSTEOMYELITIS OF THE SPINE ASSOCIATED WITH ABDOMINAL AORTIC ANEURYSM\*

## Report of a Case

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THE occurrence of an abdominal aortic aneurysm and associated Salmonella osteomyelitis of the spine seems of sufficient interest to warrant a report in some detail, together with autopsy findings.

### CASE REPORT

I P, a 69-year-old married Albanian dishwasher, was admitted to the hospital on November 10, 1945. He had apparently been in excellent health until 6 days before admission, when headaches, nausea and vomiting developed and the stools became loose but not watery. After 2 days

what with pressure and several of which had pale centers. Most of them disappeared within the first 2 hours. The heart and lungs were not remarkable. The abdomen was flaccid, with no tenderness or palpable masses. Peristalsis was active. An easily reducible left indirect inguinal hernia was present. Rectal examination revealed a moderately enlarged prostate.

The temperature was 101.2°F by rectum, the pulse 104, and the respirations 28. The blood pressure was 122/78.

Urinalysis demonstrated a +++ test for sugar and a +++ test for acetone. Examination of the blood disclosed a hemoglobin of 14.5 gm per 100 cc and a white-cell count of 10,400, with 95 per cent neutrophils. The hematocrit was 44 per cent, and the erythrocyte sedimentation rate 22 mm in 1 hour (Westergren method). The nonprotein nitro-

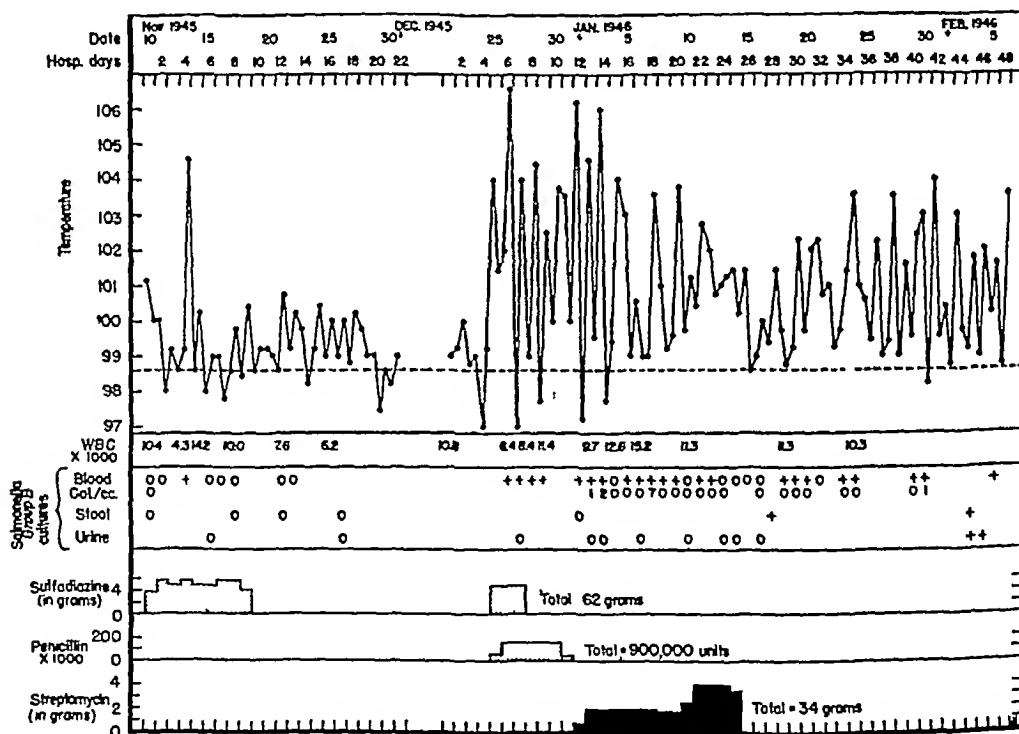


FIGURE 1 Chart, Showing Hospital Course

the bowel movements were apparently normal again. For the next 3 days he experienced several shaking chills with a maximum temperature of 103°F.

The past history revealed an inguinal hernia for which a truss had been worn for 20 years. A brother had diabetes.

Physical examination showed a well developed and well nourished man who was acutely ill, but oriented and in no great distress. He was flushed and perspiring freely. Scattered over the trunk, buttocks and thighs were about ten faintly erythematous, slightly indurated, nontender circinate areas, 1 to 4 cm in diameter, which blanched some-

when with pressure and several of which had pale centers. Most of them disappeared within the first 2 hours. The heart and lungs were not remarkable. The abdomen was flaccid, with no tenderness or palpable masses. Peristalsis was active. An easily reducible left indirect inguinal hernia was present. Rectal examination revealed a moderately enlarged prostate. The temperature was 101.2°F by rectum, the pulse 104, and the respirations 28. The blood pressure was 122/78. Urinalysis demonstrated a +++ test for sugar and a +++ test for acetone. Examination of the blood disclosed a hemoglobin of 14.5 gm per 100 cc and a white-cell count of 10,400, with 95 per cent neutrophils. The hematocrit was 44 per cent, and the erythrocyte sedimentation rate 22 mm in 1 hour (Westergren method). The nonprotein nitro-

gen was 31 mg, and the fasting blood sugar 220 mg per 100 cc. The total serum protein was 6.0 gm per 100 cc, with an albumin of 3.7 and a globulin of 2.3 gm. The blood Hinton test was negative. Cerebrospinal fluid, removed by lumbar puncture, was normal in every respect, including culture. Roentgenograms of the chest and abdomen, as well as retrograde pyelograms, were normal except for a moderate degree of calcification of the abdominal aorta. Both psoas outlines were straight and clear.

The course in the hospital is demonstrated in Figure 1.

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(Group B) Thereafter a low grade fever continued but no *Salmonella* organisms could be grown from the stool urine or further blood cultures during the first admission. Sulfadiazine was discontinued after 9 days because of no apparent benefit.

On November 21 the blood showed specific agglutination to *Salmonella* organisms (Group B) in a dilution of 1:2560 the patient's own strain of organisms being used for the test. He complained of constipation which was relieved by frequent enemas. Throughout the first hospital stay no focus of infection could be identified. The patient did not mention any back pain, but complained of discomfort in the lower part of the abdomen which was thought to be due to the hernia, and for this reason he was transferred to the Surgical Service for a herniorrhaphy.

Two days after transfer the patient was discharged because he was considered a poor surgical risk so soon after an acute infection.

The patient was readmitted to the Surgical Service for a herniorrhaphy on December 21 because of frequent cramps

finally discontinued after a total of 34 gm had been given over a period of 14 days because it neither freed the blood stream of *Salmonella* organisms nor brought the temperature to within normal levels.

At first the pain in the lower portion of the spine was present only during a spike in temperature when it was excruciating. Later it became more nearly constant. Tender ness over the same area was elicited about 4 days after the pain had first been noted and at about that time a few transient and faint erythematous spots 5 mm in diameter were observed on the abdomen. Soon thereafter the patient complained of pain in the left knee which became diffusely red and tender to deep pressure. Since a patellar click was absent and roentgenograms of the knee appeared normal no attempt was made to aspirate fluid. On January 4 1946 he fell out of bed but no known injuries resulted. At about that time he had had no bowel movements for 6 days but good results were finally obtained with an enema.

Lateral roentgenograms of the spine on January 18 showed decalcification of the anterior surface of the third lumbar

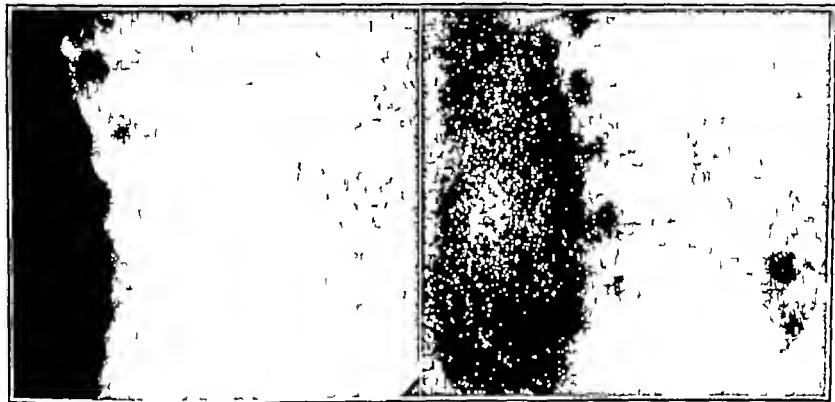


FIGURE 2 Roentgenograms of the Spine

The film on the left (taken on December 1 1945) shows a normal spine and calcification in the aorta. That on the right (taken on January 24) demonstrates a paravertebral mass displacing the aorta 2.5 cm anteriorly as well as decalcification of the anterior borders of the second and more extensively third lumbar vertebrae.

pains in the region of the hernia since discharge. The stools were loose, but no diarrhea was described.

Physical examination was essentially negative except for the hernia.

The white cell count was 10 800 other laboratory data were within normal limits. The blood Hinton test was again negative.

The temperature rose to 100°F on the 2nd hospital day and herniorrhaphy was postponed for this reason. Thereafter the temperature spiked daily three times to 106°F or over. Sulfadiazine and penicillin were given but medication was again without apparent benefit. Microscopic hematuria was noted on several examinations. *Salmonella* organisms (Group B) were repeatedly obtained on blood culture. There was no evidence of an abscess of the psoas muscle roentgenographically. A barium enema was interpreted as consistent with an inflammatory process in and around the sigmoid because of marked irritability in this region noted during fluoroscopy. The patient complained of pain in the lower portion of the spine for the first time on December 27. Lumbar puncture again gave normal findings.

Because of the persistent chills and high spiking temperature he was returned to the Medical Service on December 31 for streptomycin therapy, which he received intramuscularly every 3 hours in daily divided doses of 2 gm. This was later increased to 4 gm daily. Streptomycin was

vertebra and loss of the usual lumbar lordosis. These findings had not been present on the lateral film of the spine taken 49 days previously. X-ray films on January 24 revealed further decalcification of the third lumbar vertebra anteriorly the margins of the psoas muscles were bowed laterally and there was an area of more or less circumscribed density anteriorly from the second to the fifth vertebra displacing the sclerotic aorta 2.5 cm anteriorly (Fig 2 and 3). Films on January 29 disclosed further decalcification in the third lumbar vertebra with extension of the process to the anterior border of the second lumbar vertebra but the intervertebral space was not diminished. The psoas muscles showed further bulging.

A plaster cast was applied to immobilize the spine. By February 5 the patient had become incontinent of urine and feces and required demerol for relief of pain in the joints of the extremities. He died the next evening. Blood cultures persistently grew out *Salmonella* organisms (Group B) which were also recovered shortly before death from specimens of both stool and urine. The patient's serum agglutinated his own organisms in a dilution of 1:5120 on one occasion. Throughout the hospital stay the diabetes was well controlled with daily doses of 10 to 20 units of protamine zinc insulin.

At autopsy the peritoneal cavity contained no free fluid but along its posterior wall overlying the psoas muscles

there was a marked fluctuant bulge that was maximal over the midline and symmetrically distributed over either side, covering an area of 18 by 20 cm. There was a well defined, left, indirect inguinal hernia that admitted two fingers. The

This aneurysmal sac consisted of adventitia and opened into the aorta over an area 4.5 by 3 cm. No point of rupture could be found, but adjacent to the aneurysm there was evidence of extensive hemorrhage into both psoas



FIGURE 3 The Film on the Left (Taken on December 1) Shows Straight Lateral Margins of Both Psoas Muscles, Whereas That on the Right (Taken on January 24) Shows Marked Bulging in Both Muscles

small intestine showed no evidence of ulceration, acute inflammation or strangulation. The spleen weighed 280 gm and on cut section was deep purplish red, soft and mushy with ill defined malpighian corpuscles and markedly congested pulp. There were no verrucae or vegetations on



FIGURE 4 Autopsy Specimen, Showing Destruction of the Anterior Border of the Vertebral Body, with No Narrowing and Only Slight Involvement of the Intravertebral Space Anteriorly

any of the heart valves. The thoracic aorta showed a mild degree of atherosclerosis, and the abdominal aorta revealed marked calcification. Overlying the third lumbar vertebra, an aneurysm protruded from the posterior wall of the aorta and extended 3.5 cm inferiorly and laterally on either side

muscles. Interconnecting abscesses, filled with thick, brown, moderately foul-smelling pus lay directly posterior to the aneurysmal sac, with extensive involvement. In this area the vena cava had been invaded by a walled-off abscess, 2 by 2 cm in diameter, which projected into its lumen as a flat polypoid mass. The anterior portion of the bodies of the second and more extensively the third lumbar vertebra were necrotic and crumbly and bathed in pus (Fig 4). The psoas muscles were fusiform, dark purplish red and nearly twice their normal size, after fixation each measured approximately 23 cm in length and 9 cm in width. Multiple cross-sections showed them to be distended by an extensive blood clot, contiguous to the lateral projections of the aneurysm and measuring about 7 by 4 cm. Further sectioning of the muscles near their points of origin disclosed multiple abscesses, some interconnecting and all relatively thick walled and containing purulent material similar to that observed elsewhere. Culture grew out *Salmonella* organisms (Group B).

The brain was normal except for marked generalized arteriosclerosis. No other organs were remarkable.

## DISCUSSION

The combination of aneurysm of the abdominal aorta and *Salmonella* osteomyelitis of the spine makes this a most unusual case. The latter condition has occasionally been reported in foreign journals, but no reports could be found in the American medical literature.

Infection of the spine comprises 0.2 per cent of all cases of osteomyelitis.<sup>1</sup> Although it is usually due to tuberculosis, typhoid being the next most frequent cause, at least in the older literature, it has been reported secondary to many infections, Schmorl and Junghanns<sup>1</sup> giving references to papers reporting twenty-five different etiologic organisms.

There are conflicting reports regarding the frequency of osteomyelitis as a complication of Salmonella infection. In 1382 cases of paratyphoid infection, Webb-Johnson<sup>2</sup> was able to recover the organism from bones or joints only twice, although many of the patients had painful joints in which the aspirated fluid was sterile. Seligmann<sup>3</sup> reported only 3 cases with osteomyelitis out of 1000 bacteriologically proved Salmonella infections. These were due to organisms from Group B (*Salmonella typhimurium*) and Group D (*S. enteritidis* and *S. panama*), although those in Group C (specifically *S. choleraesuis*) are supposedly more invasive for human beings. Harvey,<sup>4</sup> reviewing the literature on the last organism, found 15 of 71 patients (over 20 per cent) to have manifestations of involvement of the bones or joints. He did not, however, specifically state that organisms were recovered from these bones or joints. He also mentioned a current hospital case of osteomyelitis of the spine but did not report it in detail. This is the only reference of this condition found in the American medical literature. In the case reported above the Salmonella infection may have involved the knee as well as the spine, although no culture was taken of the former.

For a better understanding of the two fundamentally different types of pathologic processes in the vertebral bodies (infection and pressure erosion) an attempt is made to reconstruct the sequence of events as they occurred in this patient. It is postulated that the aneurysm of the abdominal aorta leaked out blood, providing a culture medium and finally resulting in a prevertebral abscess. The erosion of the vertebral bodies was probably started directly by the aneurysm and continued by the transmitted aortic pulsation through the prevertebral abscess, which developed between the aneurysm and the vertebrae. Only later did the infection spread through the wall of the abscess and actually invade the bone. Although the evidence is incomplete, the data are all in support of this thesis.

As for the aneurysm, its origin could have been syphilitic, mycotic or arteriosclerotic.

Although aortic aneurysms are usually syphilitic, those below the renal arteries, as in the case reported, are rarely due to *Treponema pallidum*. Furthermore, this patient had several negative serologic tests for syphilis during life, and no autopsy findings were suggestive of the disease.

The possibility of a mycotic aneurysm must be seriously considered. Such aneurysms usually result from infections from within, 90 per cent being due to subacute bacterial endocarditis or subacute bacterial endarteritis, secondary to a congenital vascular anomaly such as patent ductus arteriosus or coarctation of the aorta. Stengel and Wolferth<sup>5</sup> collected 217 cases of mycotic aneurysm of which 187 were due to subacute bacterial endocarditis. Of the remaining 30, the authors state that 6 were "associated" with osteomyelitis, but no mention is

made of which bones or vessels were involved or whether the aneurysm was adjacent to the osteomyelitis in any of the cases. Thus it is not known if the aneurysms were produced by direct extension or by infected emboli in these cases. Apparently the only reported cases of mycotic aortic aneurysms due to direct extension from osteomyelitis of the spine were in patients with Pott's disease. Interestingly enough, Klotz<sup>6</sup> does not refer to direct extension mycotic aneurysms due to osteomyelitis in his monograph on aneurysms, and Osler<sup>7</sup> does not even mention direct extension mycotic aneurysms of any kind in his long chapter on aneurysms, even though he is said to have been the first to adopt the term "mycotic."

It is unlikely that the case described above had a mycotic aneurysm from within, since there was no subacute bacterial endocarditis; however, it is not completely impossible that an infected embolus was lodged there after Salmonella bacteremia. It is also very unlikely that this was a mycotic aneurysm from without, by direct extension of the infected vertebral body, because at autopsy the wall of the aneurysm was found to consist of adventitia.

Arteriosclerotic aneurysm therefore seems the most tenable etiology in this case. Kampmeier,<sup>8</sup> in reviewing the literature on abdominal aortic aneurysms in 1936 collected 313 cases and added 68 more. Of these he considered "very few" to be arteriosclerotic, the great majority being syphilitic. However, more recently in other series incidences of 21 per cent (20 of 96 cases)<sup>9</sup> and 17 per cent (8 of 48 cases)<sup>10</sup> have been reported, indicating that such an etiology is not uncommon. The evidence of marked calcification of the abdominal aorta, as well as of other arteries visible in the x-ray films and at autopsy, the microscopical picture of the aorta and the patient's diabetes all support the arteriosclerotic etiology.

Erosion involving the anterior portion of the vertebral bodies and sparing the intervertebral structure is typical of external pressure as seen most commonly from aortic aneurysms, and not of an infectious process. When looked for, vertebral erosion secondary to abdominal aortic aneurysm is often seen.<sup>8-10</sup> Farmer<sup>11</sup> reported such a case with striking ante-mortem roentgenograms of the spine and pictures of the spine removed at autopsy. In the Army Medical Museum at Washington, D. C., there is a specimen of four adjacent vertebral bodies with erosion due to aortic aneurysm. The erosion may become so marked as to result in compression of the spinal cord by the aneurysm.<sup>11, 12</sup>

In contrast, infections of the spine do not usually begin in the central or anterior portion of the vertebral body but in the intervertebral space and adjacent bony surfaces.<sup>13-16</sup> The earliest x-ray changes are narrowing of the intervertebral space caused by destruction of the intervertebral tissues, as well



as questionable involvement of the adjacent bone. This narrowing is usually asymmetrical, resulting in a kyphoscoliosis and a loss of the usual lumbar lordosis, which is also due in part to muscle spasm. The reports of *Salmonella* spondylitis in the foreign medical literature indicate that it usually occurs in the lumbar spine and follows the typical course of any infectious spondylitis. Healing by ankylosis is the rule. Ssokoloff<sup>16</sup> was able to collect 5 such cases due to *Salmonella*, and reports of 6 others were found.<sup>1, 12, 14, 16, 17, 18</sup> It is interesting in passing to note the rarity of psoas abscess associated with nontuberculous osteomyelitis of the spine, which this patient had. In fact, Hesse<sup>14</sup> could not find a report of any such case, although the abscesses do occur in staphylococcal osteomyelitis of the spine.

### SUMMARY

A case of abdominal aortic aneurysm and adjacent *Salmonella* osteomyelitis of the spine with autopsy findings is reported.

An attempt is made to analyze the sequence of events occurring in this case.

It is concluded that the abdominal aortic aneurysm was primary and arteriosclerotic in origin, whereas the *Salmonella* osteomyelitis of the spine developed secondarily.

A review of the literature reveals that *Salmonella* osteomyelitis of the spine is very uncommon, and this is apparently the first case in which either aneurysm or psoas abscess was found associated with this condition.

Streptomycin, given over fourteen days in a total dose of 34 gm, apparently had no effect whatsoever on the *Salmonella* infection.

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# BONE AND JOINT PAIN IN LEUKEMIA, SIMULATING ACUTE RHEUMATIC FEVER AND SUBACUTE BACTERIAL ENDOCARDITIS\*

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**A**LTHOUGH pain along the bones and in the joints in the acute leukemias has been reported in the literature from time to time, its diagnostic significance has not been sufficiently stressed and its confusion with acute rheumatic fever has been the rule rather than the exception. This confusion has depended to a large extent upon the many similarities in the symptomatology of the leukemias and rheumatic fever. In either of these conditions there may be asthenia, palpitation, dyspnea on exertion, epistaxis, fever, bone and joint pain, abdominal pain, pallor, purpuric manifestations, lymphadenopathy, splenomegaly, anemia, tachycardia, accentuation of the heart sounds and cardiac murmurs. Additional diagnostic difficulties arise in the early stages of leukemia when lymphadenopathy, splenomegaly, hepatomegaly and a clear-cut blood picture may be absent. The importance of a correct diagnosis can be appreciated especially from the standpoint of management and prognosis.

Although it is not our purpose to review the entire literature pertaining to this subject, mention of a few of the outstanding contributions is made. That pain and tenderness along the bones and in the joints constitute a prominent feature of the symptomatology of the leukemias was pointed out as early as 1889 by Ebstein<sup>1</sup> and 1895 by Fraenkel.<sup>2</sup> In 1913 Strauch<sup>3</sup> again mentioned that in some cases of acute lymphatic leukemia the onset is marked by pain, and swelling of the joints, resembling articular rheumatism. Seward<sup>4</sup> reported a case in a thirty-one-year-old man who died of lymphatic leukemia and who presented during life severe pain and swelling of the hips and shoulders. Poynton and Lightwood<sup>5</sup> described a case in a three-and-a-half-year-old girl with acute lymphatic leukemia and multiple, migratory joint pain recorded as "fitting from joint to joint," and involving the ankles, knees, wrists and fingers. In a series of 28 cases of leukemia in children reported by Wollstein<sup>6</sup> pain over the bones occurred in 10. In a larger series studied by Cooke<sup>7</sup> 13 out of a total of 50 patients had "rheumatoid pain," which was the most prominent symptom in 6 cases. Baldridge and Awe<sup>8</sup> found acute arthritis in 13 of 20 patients under twenty-one years of age with lymphogenous leukemia. Similar reports have appeared by Smith,<sup>9</sup> Sutton and Bosworth,<sup>10</sup> Conybeare<sup>11</sup> and others.

It is interesting to note that in the majority of the reported cases the diagnosis of rheumatic fever was originally made.

The coexistence of leukemia and rheumatic fever has been regarded as extremely rare. Ehrlich and Forer<sup>12</sup> reported a fatal case in an eleven-year-old girl with acute myelogenous leukemia, who presented pain, tenderness, redness and swelling about the joints, so that the condition seemed indistinguishable clinically from acute rheumatic fever. At autopsy the heart showed both leukemic infiltration and Aschoff bodies. No similar case, according to the authors, was found in the literature.

Occasionally, the articular manifestations of the leukemias simulate rheumatoid arthritis. This is particularly so in patients presenting fusiform swelling of the proximal interphalangeal joints of the fingers. Such cases have been reported by Karelitz<sup>13</sup> and Flinn.<sup>14</sup> Differentiation from Still's disease, which may be accompanied by generalized enlargement of the lymph nodes and by splenomegaly, is important in children.

Foraker<sup>15</sup> has classified bone and joint involvement in the leukemias under the following headings: tumor-like lesions of bones in chloroma, tumors of leukoblastic origin in bones and destructive and absorptive lesions leading to softening, defects and fractures, periosteal elevations, particularly about the joints, arthritis, often of the acute recurrent type, more rarely of the chronic infectious type, osteosclerosis of the bone marrow, and osteomyelitis. Some overlapping of these categories frequently occurs. Patients with acute arthritis, for example, often show periosteal elevations on x-ray study.

Pathologically, apart from tumor formation, leukemic infiltration has often been demonstrated in cases showing periosteal elevations. However, not all patients who exhibit joint pain during life present articular changes on pathological examination. In the report by Seward<sup>4</sup> of severe joint pain during the course of lymphatic leukemia no gross or microscopical abnormalities of the joints were found on post-mortem study. Baldridge and Awe<sup>8</sup> were able to demonstrate lymphoblastic infiltration of bone in 1 of 55 cases of lymphogenous leukemia and in 1 of 14 cases of subleukemic lymphogenous leukemia.

This report presents 4 cases of acute lymphatic leukemia in which bone and joint pain were outstanding features. In 2 cases a diagnosis of acute rheumatic fever was made at the time of admission to the hospital. In a third case the findings so

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closely resembled those of subacute bacterial endocarditis that this diagnosis was made on entry. The fourth case was correctly diagnosed on admission, but it is interesting to note that the referring physician considered the symptoms rheumatic in origin. These cases fall into the fourth (arthritic) category of Forkner,<sup>15</sup> cited above.

### CASE REPORTS

**CASE 1\*** J G (R B B H 1849), a 7-year-old girl, was admitted to the hospital on July 18, 1939, with a complaint of pain and tenderness in the right knee of 4 weeks' duration. She had had several episodes of migratory joint pain, involving the knee, elbows and ankles and the cervical and lumbar areas of the spine. On one occasion the right elbow joint had remained swollen for 3 days. She also complained during this period of recurring, transient, right-lower-quadrant pain associated with nausea and on several occasions with vomiting. There had been a slight nonproductive cough. The temperature had varied between 99 and 100°F, and the pulse between 100 and 140.

An aunt was said to have a "leaking valve," and another was known to have definite rheumatic heart disease.

On physical examination the patient did not appear to be acutely ill. There was a slight malar flush. No lymphadenopathy was present. Examination of the heart showed no enlargement, a forceful apical beat and a reduplicated pulmonic second sound. There were no murmurs or thrills. The tip of the spleen was palpable at the end of deep inspiration. The right knee was painful on motion, permitting flexion to 90°.

The temperature was 99.5°F, and the pulse 135. The blood pressure was 105/75.

Examination of the blood disclosed a red-cell count of 4,560,000, with a hemoglobin of 80 per cent, and a white-cell count of 5550, with 49 per cent neutrophils, 50 per cent lymphocytes and 1 per cent basophils. The platelets appeared normal in number.

During the hospital stay the patient experienced several episodes of fleeting joint pain involving the elbows, knees and ankles. She also complained frequently of lower abdominal pain, associated at times with nausea and vomiting. At the end of 10 weeks the liver and spleen were readily palpable, and the blood revealed the development of a moderate secondary anemia. There was a progressive rise in the percentage of lymphocytes and a fall in the number of platelets. Because of the progressive anemia, blood transfusions were resorted to. This procedure aided in maintaining the hemoglobin level between 80 and 85 per cent and the red-cell count between 4,000,000 and 4,500,000. The white-cell count varied between 4000 and 5000. On smear 90 per cent of the cells were lymphocytes. Fourteen weeks after admission purpuric spots appeared over the body, and a few large ecchymoses were noted. The cervical, axillary and inguinal nodes became enlarged. The hemoglobin level had fallen to 57 per cent, the red-cell count to 3,610,000, and the platelet count to 58,000. At the end of 16 weeks there was a further drop in the hemoglobin to 35 per cent, in the red-cell count to 2,080,000 and in the platelets to 15,000. The white-cell count was 3950, and on smear only lymphocytes were seen, of which 60 per cent were classified as large and the remainder as blast and atypical forms. Considerable bleeding from the gums took place, and on one occasion hematemeses occurred. Terminally there were repeated convulsions, and the respiratory rate reached 68 per minute, and the pulse rate 160 per minute. The patient died approximately 18 weeks after admission.

Permission for autopsy was not obtained.

**CASE 2** J MacR (B C H 862,131), a 19-year-old boy, was admitted to the hospital on June 1, 1937. He had been well until 8 weeks before entry, when he had experienced episodes of vomiting continuing over a period of 4 weeks. Four weeks prior to admission he had complained of steady pain in the right shoulder and in the joints of the right foot, the latter associated with local swelling and tenderness and

severe enough to make weight bearing impossible. On the day of entry he had had two moderately severe nosebleeds.

Except for vague muscular pains during the last year, the past history was noncontributory.

On physical examination the skin and mucous membranes were moderately pale, but otherwise not remarkable. Venous and arterial pulsations in the neck were very prominent. The throat was injected. The heart sounds were of booming quality, with accentuation of the pulmonic second sound. A loud, harsh, systolic murmur was heard along the left border of the sternum, best at the second left interspace. The liver and spleen were not palpable. There was slight local swelling, redness and heat over the bones of the right foot, with definite tenderness on pressure. Examination of the right shoulder was negative.

The temperature was 99.6°F, and the pulse 90. The blood pressure was 120/64.

Examination of the blood revealed a red-cell count of 2,050,000, with a hemoglobin of 38 per cent, and a white-cell count of 13,400, with 48 per cent neutrophils, 50 per cent lymphocytes and 2 per cent monocytes.

Because of the marked anemia the patient received several blood transfusions, with little response in either the hemoglobin level or the red-cell count. He continued to have repeated, moderately severe nosebleeds while on the ward. He complained considerably of pain in the joints of the right foot and later of generalized joint pain, especially marked in the left elbow, which had become moderately swollen and very tender to touch. The value for blood uric acid was 18.5 mg per 100 cc. On the 23rd hospital day the white-cell count was 7600, and the smear showed 50 per cent lymphocytes. The liver and spleen were now palpable, and their size increased rapidly up to the time of death. On the 29th day the white-cell count had risen to 144,000, with 29 per cent lymphocytes, mostly immature forms. There was generalized enlargement of the lymph nodes. Acute ulcerations of the mucous membranes of the mouth developed, and the patient died suddenly on the 37th hospital day.

Autopsy† revealed leukemic infiltration of the spleen, liver, kidney, anterior mediastinal connective tissue, lymph nodes, and lumbar, sternal, femoral and tibial bone marrow. Small collections of lymphocytes were found in the synovia of the left elbow joint. The renal tubules were packed with deposits of uric acid.

**CASE 3** R C (B C H 919,897), a 15-year-old schoolboy, was admitted to the hospital on November 11, 1938. One month before entry migratory joint pain involving the right knee, left ankle, wrists and elbows had developed. The joints were warm, painful on motion and tender to touch, but not remarkably swollen. These symptoms persisted for 1 week, after which he noticed progressive pallor of the skin. He became feverish, and for the first time experienced night sweats. Two weeks after the onset of the illness he complained of soreness of the finger tips, aggravated by pressure. On the day prior to entry he had an episode of sudden blurring of vision in the left eye, which rapidly cleared up. Except for palpitation, he offered no additional complaints.

Physical examination disclosed a patient who appeared acutely ill. The skin had a definite café au lait color. The throat was moderately injected. The apical beat was diffuse and forceful, and the left border of cardiac dullness was percussed just outside the midclavicular line. The heart sounds were rapid and booming, and the pulmonic second was greater than the aortic second sound. A loud, blowing systolic murmur was heard at the apex. The spleen was felt two fingerbreadths below the left costal margin. The liver was not palpable. A few, small cervical, axillary and inguinal nodes were found. There were no petechiae. The joints were normal.

The temperature was 101°F, and the pulse 120. The blood pressure was 108/72.

Examination of the blood showed a red-cell count of 1,520,000, with a hemoglobin of 30 per cent, and a white-cell count of 3800, with 10 per cent neutrophils, 16 per cent small lymphocytes, 6 per cent large lymphocytes, 67 per cent lymphoblasts and 1 per cent monocytes. The platelet count was 45,000. Repeated blood cultures were negative. An electrocardiogram was interpreted as indicative of myocardial damage. X-ray examination of the chest was negative.

\*We are indebted to Dr. Marshall G. Hall of the Robert Breck Brigham Hospital, for permission to report this case.

†Boston City Hospital No. 37-64.

The course was progressively downhill. On the 2nd hospital day considerable hemorrhage occurred from the gums and on the 3rd day there was a retinal hemorrhage in the left eye. Repeated blood transfusions had no effect on the hemoglobin level or the red-cell count. The white-cell count rose to 20,000 on the 3rd day, and fell to 4,200 by the 6th day. The temperature remained elevated throughout the illness and was septic in type. The patient died on the 18th hospital day. The white-cell count prior to death was 3,800 with no essential changes in the blood smear.

Permission for autopsy was not obtained.

**CASE 4.** M. W. (B. C. H. 870 403), a 14-year-old Negroess was admitted to the hospital on August 19, 1937, too ill to give a satisfactory history. From the mother it was learned that the patient had complained for the past year of weakness and fatigability. For 7 weeks prior to admission there had been considerable joint and muscle pain, and for 4 weeks slight intermittent bleeding from the nose and gums. Three months previously she had had a severe sore throat which had improved after 1 week. Amenorrhea had been noted for the last three months.

Physical examination disclosed a patient who appeared acutely ill complaining mostly of abdominal pain. The mucous membranes were very pale. There was evidence of recent bleeding from the gums. The tonsils were red, large and ulcerated. A few small nontender lymph nodes were felt in the neck. Moist rales were heard at both bases. The heart sounds were of booming quality and a loud systolic murmur was heard at the apex. The liver edge was palpated six fingerbreadths, and the spleen three fingerbreadths below the costal margin. A round tender mass was felt supra-pubically consistent with a pregnancy of 4 months duration. The blood pressure was 110/58.

Examination of the blood showed a red-cell count of 1,330,000 with a hemoglobin of 28 per cent and a white-cell count of 278,000. The white cells on smear were predominantly immature lymphocytes. There was a marked reduction in the number of platelets.

During the brief hospital stay the patient complained of constant, generalized abdominal pain. She died suddenly approximately 15 hours after admission.

Autopsy\* revealed leukemic infiltration of the spleen, liver, pancreas, stomach, ileum, kidney, adrenal glands, ovaries and uterus and vertebral costal sternal femoral and tibial bone marrow, as well as lymph nodes throughout the body. The joints were not examined. The uterus contained a fetus estimated to be 18 weeks old, whose tissues were free of leukemic invasion on microscopical examination.

## DISCUSSION

The cases presented above illustrate very clearly the similarities in the symptomatology and physical signs, at certain stages, of leukemia, acute rheumatic fever and subacute bacterial endocarditis. Although numerous reports in the literature demonstrate the similarities between leukemia and acute rheumatic fever, little reference to the difficulty in differentiating leukemia from subacute bacterial endocarditis is to be found. However, the fact that confusion between these two diseases has occurred is brought out in the following statement by Herrick<sup>14</sup>:

I do not remember to have seen malignant endocarditis mistaken for acute leukemia, but I have seen the latter looked upon as malignant endocarditis. The fever rapidly developing anemia, the hemorrhagic lesions in the skin, the enlarged spleen and a loud endocardial murmur may make the resemblance quite strong.

The various symptoms and signs common to these illnesses may be listed as weakness, fatigability, weight loss, fever, sweats, bone and joint pain,

muscle pain, painful fingertips, abdominal pain, anorexia, vomiting, epistaxis, pallor, shortness of breath, palpitation, anemia, hemorrhagic skin lesions, tender, warm, swollen joints, lymphadenopathy, splenomegaly, tachycardia, accentuation of heart sounds and cardiac murmurs. Certain clinical findings merit further comment regarding differential diagnosis.

## Blood Picture

It should be remembered that anemia and thrombocytopenia are not essential features of the early stages of leukemia. Hence, the finding of normal values for hemoglobin and normal counts for red cells and platelets does not exclude leukemia as a diagnosis. This is clearly demonstrated in Case 1, in which the hemoglobin was 80 per cent, the red-cell count 4,560,000 and the platelets normal a month after the onset of symptoms. Later in the course of the disease anemia and thrombocytopenia become prominent, attaining a severe grade in most cases. The degree of anemia, when present, is only of limited value in differential diagnosis. According to Wilson<sup>17</sup> secondary anemia is usually present during rheumatic activity, and its degree parallels the severity and duration of the disease. In a series of cases from the New York Hospital the average red-cell count was 3,700,000, and the range from 2,800,000 to 4,500,000. The anemia is usually not severe enough to warrant blood transfusions, unless repeated and severe nosebleeds have occurred. In the presence of profound degrees of anemia and findings simulating acute rheumatic fever leukemia must be considered in the differential diagnosis. Cases 3 and 4 illustrate this point, the red-cell count in the former having been 1,500,000 and that in the latter 1,300,000 at the time of admission to the hospital. The difficulty in differential diagnosis based on this point, however, is well shown by Case 2, in which repeated and severe epistaxes occurred and in which the red-cell count on admission was 2,050,000. That diagnosis cannot always be made on a single finding is again brought out by Poynton's<sup>18</sup> mention of a rare case of rheumatic fever in which the anemia proved fatal. Severe anemia in rheumatic fever has also been reported by Hubbard and McKee.<sup>19</sup>

The response of the anemia to blood transfusion is not in itself diagnostic. Although, generally speaking, the anemia in leukemia does not respond readily to this procedure, especially in the presence of hemorrhage, a fair response may be obtained in the early stages of the illness, as in Case 1, in which the hemoglobin level was brought up from 63 per cent to 85 per cent within a period of three weeks. Later in the course of the disease transfusions were of no avail.

The presence or absence of leukocytosis may be of some aid in diagnosis. Leukocytosis is the rule in cases of active rheumatic fever associated with

\*Boston City Hospital No. 37 542.

joint pain<sup>20</sup> The average white-cell count, according to Wilson,<sup>17</sup> is 13,200, the range being from 8000 to 23,000 In 91 per cent of her cases the white-cell count was over 9000 Consequently, the presence of leukopenia associated with symptoms referable to the bones and joints should make one suspect conditions other than acute rheumatic fever The differential count is of great importance Ordinarily, there is a rise in the percentage of neutrophils during active rheumatic fever<sup>20</sup> The finding of lymphocytosis, especially when associated with leukopenia, is presumptive evidence against rheumatic fever, even though the clinical manifestations point to that diagnosis Cases 1 and 2, both of which presented leukopenia and moderate lymphocytosis, were erroneously considered to be acute rheumatic fever at first No difficulties arise in differential diagnosis when the blood picture is what is usually considered more typical of leukemia

### *Joint Pain*

Any group of joints may be involved in either leukemia or acute rheumatic fever The clinical features of one may be indistinguishable from those of the other There may be transient arthralgias, migratory joint pain, persistent pain in one or more joints and all the local manifestations of heat, redness and swelling The response of the joint pain to salicylates does not help in distinguishing one disease from the other Although cases have been reported in which salicylates have failed to relieve the joint pain in leukemia,<sup>21</sup> the patient in Case 1 obtained definite benefit from them

The determination of the level of blood uric acid may be of decided value in the differential diagnosis of the two diseases In conditions like leukemia, in which there may be considerable destruction of blood and liberation of nucleoproteins, the value for blood uric acid may become elevated, in some cases markedly so The blood level in Case 2 was 18.5 mg per 100 cc, and at post-mortem examination the renal tubules were packed with deposits of uric acid Hench<sup>22</sup> brought out the point that the acute arthritis in leukemia should be suspected as gouty Unfortunately, values for uric acid were not obtained in the other cases reported above Hyperuricemia is not present in acute rheumatic fever

### *X-ray Films of Bones and Joints*

Numerous reports have appeared in the literature concerning bone and joint changes as visualized by x-ray examination in cases of leukemia An excellent review of the literature on this subject is presented by Connor<sup>23</sup> Among the changes noted were subperiosteal elevation, osteosclerosis, osteoporosis, cortical stratification, rarefaction at the ends of the long bones, spontaneous fractures, large tumor masses in the upper ends of the long bones, various osteolytic lesions and medullary striations These lesions are produced essentially by the encroachment

of leukemic cells on the normal bony structures All cases of leukemia, however, do not show bone changes on x-ray study In a review by Wollstein<sup>6</sup> of 10 cases of leukemia in children presenting bone and joint pain as a symptom, x-ray evidence of bone changes was found in 6, consisting of cortical destruction, rarefaction and periosteal elevation X-ray studies of all the bones in Case 1, taken eight weeks after the onset of the illness, were entirely negative The commonest x-ray finding is periosteal elevation It should be realized that this abnormality is far from specific for the leukemias It may be seen in a number of different conditions, among them osteomyelitis, scurvy, congenital syphilis and bone tumors The cause of pain in the joints and along the bones in cases of leukemia is generally attributed to the invasion of the bony and articular structures by leukemic cells, although such invasion has not been consistently demonstrated No satisfactory explanation why this symptom is more frequent in younger patients has been given

In conclusion it is emphasized that the presence of bone and joint pain, apart from that of traumatic origin, in young people does not invariably mean acute rheumatic fever The differential diagnosis of this symptom should include a consideration of many conditions, among them undulant fever, poliomyelitis, osteomyelitis, scurvy, rickets, syphilis, gonorrhea, tuberculosis, Haverhill fever, Hodgkin's disease and Still's disease A discussion of the differential diagnosis of these conditions is beyond the scope of this paper We have simply attempted to demonstrate the similarity in the symptoms and signs of leukemia and acute rheumatic fever, and to point out certain features that may be of value in their differential diagnosis, especially in the earlier stages of leukemia when the usual typical features may be lacking

### SUMMARY

Four cases of acute lymphatic leukemia, 3 presenting signs and symptoms simulating those of acute rheumatic fever and 1 simulating those of subacute bacterial endocarditis, are presented

Certain pitfalls and aids in the differential diagnosis between acute rheumatic fever and acute lymphatic leukemia are discussed

Complete examination of the blood should be performed routinely in all cases presenting bone or joint pain as a symptom

The findings that point to the diagnosis of lymphatic leukemia rather than of acute rheumatic fever are leukopenia persistent in the presence of an active clinical course, leukopenia or leukocytosis associated with an increase in the percentage of lymphocytes and bone changes on x-ray examination

The various bone changes in leukemia visible by x-ray study are enumerated

The importance in differential diagnosis of other disorders that cause bone and joint pain in young people is mentioned

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## MEDICAL PROGRESS

### ORTHOPEDIC SURGERY

#### II Growth and Inequality of Leg Length in Poliomyelitis\*

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ALTHOUGH it is not the purpose of this paper to consider in detail the general factors that as a rule affect equally the growth of both limbs, a few words about normal growth may not be amiss.

Nature produces regularly in the human being, as in many other animals, paired, symmetrical, mirror-imaged extremities of essentially identical length. These normal growth processes are complex and dynamic, beginning with the union of an ovum and a sperm, which carry in their chromosomes the hereditary factors (genes) that determine whether the person will have the muscular legs of an athlete, the shapely limbs of the chorus girl or the misshapen contours of the achondroplastic dwarf.

Added to the hereditary are many environmental factors that affect normal development. The diet of the pregnant mother<sup>1, 2</sup> and of the child during its whole growing period is of great importance.<sup>3</sup> Vitamins, proteins, minerals and carbohydrates are needed in adequate amounts. The pituitary, thyroid, adrenal and other glands of internal secretion furnish hormones that directly or indirectly play an important role in determining the physical characteristics of the person and of his lower extremities.

The over-all length of the lower limbs consists in the length of the femur and tibia, with some minor increments represented by the articular cartilage of the hip, knee, ankle and subastragalar joints and by the bones of the hind foot (os calcis and talus).

Longitudinal growth of the long bones is the result of the highly specialized activity of the epiphyseal plates. Cartilage cells arranged in columnar fashion multiply, pushing the epiphysis at either end of the bone away from the diaphysis. At the same time the older cells of the epiphyseal plate nearest the diaphysis mature and are replaced by bone. Thus, during the growing period, the cartilage plate maintains an approximately constant thickness while the shaft of the bone increases in length. At some time in adolescence the growth potential of the epiphyseal plate becomes exhausted, the cartilage cells reach senescence and die, and the diaphysis unites with the epiphysis, leaving at most a faint transverse x-ray shadow to indicate the site of the epiphyseal plate. According to Green<sup>4</sup> the average skeletal age for cessation of longitudinal growth of the femur and tibia is fourteen years and three months in girls and sixteen years and three months in boys. There are wide variations from this average, which become less pronounced if true skeletal age is substituted for chronologic age. For the determination of skeletal age, the work of Todd<sup>5</sup> on skeletal maturation has given a reasonably satisfactory set of standards.

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There is cessation of growth long before fusion of the epiphysis and diaphysis occurs. Although x-ray films may show the epiphyseal line to be open, all growth from that cartilage plate may have ceased.

The epiphyseal plates of the femur and tibia do not contribute equally to the longitudinal growth of

TABLE 1 *Contribution of Femoral and Tibial Epiphyses to Longitudinal Growth of the Lower Extremity*

EPIPHYSIS	BONE LENGTH CONTRIBUTED		APPROXIMATE LEG LENGTH CONTRIBUTED	
	%*	%†	%‡	%‡
Proximal femur	30	30	16	
Distal femur	70	70	39	
Proximal tibia	55	56	25	
Distal tibia	45	44	20	

\*According to Gill and Abbott \*

†According to Green and Anderson †

‡Calculated from Green and Anderson ‡

the lower extremity. Although exact values derived from observation of a large series of cases are not available, the figures presented in Table 1 appear to be reasonably accurate.

### UNEQUAL GROWTH

Many conditions may result in asymmetrical growth and unequal length of the legs. These conditions may be classified in three main groups

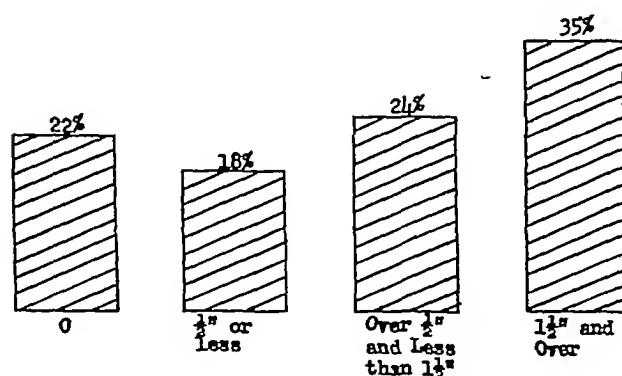


FIGURE 1 *Incidence of Discrepancy in Leg Lengths among 371 Cases of Poliomyelitis in Which the Onset Occurred before the Age of Sixteen Years*

growth retardation due to local interference at an epiphyseal plate, growth retardation due to interference from remote causes, and factors that may stimulate unilateral growth.

### Local Interference at an Epiphyseal Plate

Congenital abnormalities of the epiphyseal plate, tumors, infections and trauma are some of the more important types of pathologic processes that can directly impair the ability of an epiphyseal plate to keep pace with its counterpart.

A few children are born with congenital abnormalities in which one or more epiphyseal plates are absent or deficient. Osteomyelitis or tumor may invade an epiphyseal plate, destroying the cartilage cells and thus causing unequal growth. A fracture through an epiphysis may cause premature union of the epiphysis, with resultant shortening of the extremity.

### Interference from Remote Causes

Any process that results in unequal motor power in the two extremities may cause unequal growth. Poliomyelitis is the most important member of this class, which also includes spastic, obstetric and traumatic nerve palsies. The flaccid paralysis of poliomyelitis, obstetric and traumatic nerve lesions is associated with much more shortening than is found in spastic paralysis.

Disuse is a potent cause of growth retardation. Prolonged immobilization of an otherwise normal extremity may cause retardation of growth and premature ossification of normal epiphyseal plates. Numerous observers have noted that tuberculosis of the hip treated by prolonged immobilization of the whole extremity in a plaster cast results in extreme atrophy and shortening of up to 4 or 5 inches. Recently, attention has been called to the fact that this may be due to premature closure of the epiphyses about the knee.<sup>7, 8</sup>

Another example of the effect of unilateral immobilization on growth may be cited. Cases of unilateral Legg-Perthes disease, treated by prolonged bed rest but with little or no immobilization of either extremity, recover with minimal shortening—usually not exceeding 1 cm. This minimal shortening is probably due to local interference with growth at the proximal femoral epiphysis. But a similar series of cases, in which the affected leg was protected by a nonweight-bearing brace for an equally prolonged period, showed more shortening (1 to 3 cm) than those treated by bed rest. It is well known that growth and form are directly influenced by function. It is therefore equally true that disuse or restricted use of one extremity will adversely affect its development.

### Unilateral Growth

Unilateral stimulation of growth occurs rarely. The conditions in which it most often occurs are osteomyelitis, vascular tumor such as hemangioma, arteriovenous fistula and fracture of the diaphysis of growing bones. The common denominator appears to be increased blood supply to the affected ex-

trinity, giving a favorable environment for rapid growth of the epiphyseal plates

#### EFFECT OF POLIOMYELITIS ON GROWTH OF LOWER EXTREMITIES

In the preparation of this paper, the records of 700 cases of infantile paralysis treated in the Out Patient Department of the Massachusetts General Hospital were reviewed. Of 371 cases in which the onset was before the age of sixteen, 41 per cent had  $\frac{1}{2}$  inch or less of shortening, 24 per cent had over  $\frac{1}{2}$  inch but less than  $1\frac{1}{2}$  inches, and 35 per cent had  $1\frac{1}{2}$  inches or more of shortening (Fig 1)

It will be apparent that these figures give an abnormally high incidence of shortening. They pertain to patients in the Out Patient Department with sufficient residual crippling to warrant their seeking

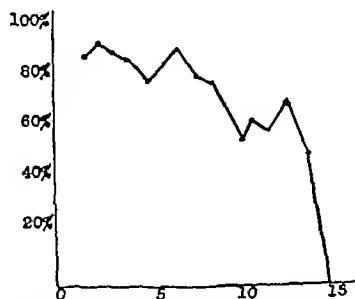


FIGURE 2. Percentage of 371 Patients Developing Shortening of  $\frac{1}{4}$  Inch or More

medical help. In the poliomyelitis population as a whole the gross incidence of shortening must be considerably lower than the figures from this clinic.

#### Age at Onset

It will be obvious to the most casual observer that the age at onset must be an important factor in the production of discrepancy in leg length.

Adults who develop poliomyelitis can be expected to develop no discrepancy in leg length. But the infant, upon whom the growth retarding effect of poliomyelitis may act for the rest of his growing years, has a real chance of developing inequality in length (Fig 2 and 3).

#### Sex

Inequality in leg length of moderate or marked severity is more frequent in boys than in girls (Fig 4).

The growing epiphyses of the lower extremities close approximately two years earlier in girls than in boys. Therefore, the retarding effect of polio-

myelitis has a shorter time in which to act on the growing epiphyses of the former. Also the average adult leg length is less in the female than in the male, and therefore a percentage retardation of

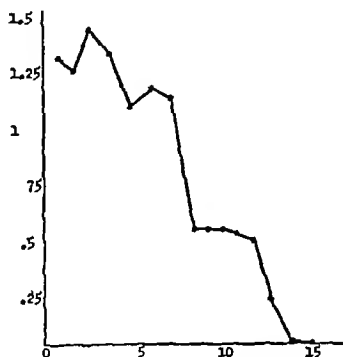


FIGURE 3. Average Shortening in Inches among 371 Patients

growth should produce less actual discrepancy in length in the female than in the male.

#### Muscular Weakness

Discrepancy in adult leg length in poliomyelitis is practically invariably associated with asymmetrical

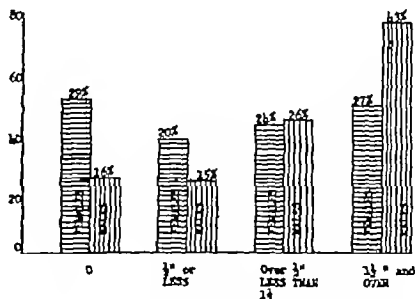


FIGURE 4. Shortening of Leg among 191 Female and 180 Male Patients

paralysis. In the cases under consideration no significant shortening was found in patients with symmetrical motor power. Whether the legs were totally paralyzed, partially paralyzed or normal, the



legs were essentially equal in length, provided the involvement was bilateral and symmetrical

The greatest amount of shortening occurred in cases in which there was one essentially normal leg and one totally paralyzed and in which the onset was at an early age. In every case in which there was one normal and one severely paralyzed leg, and in which the age at onset was under ten years, marked shortening occurred

#### *Amount of Shortening to be Expected*

No really accurate tables for the prediction of individual normal growth have been worked out. It is therefore improbable that an exact formula can be devised that will allow accurate long-range prediction of the amount of shortening to be expected in any given case of poliomyelitis. The multiplicity of variable factors affecting normal growth, in addition to those due to the disease, complicates the problem still further.

The growth curve for an individual patient is rarely smooth, since growth is not at a constant rate. Illness and health, use and disuse, winter and summer, and many other factors are involved.

In 1 case (Case 41402), in which poliomyelitis occurred at the age of five, the discrepancy in leg length, as indicated by clinical measurement, appeared to occur throughout the growing period. One leg was essentially normal in muscle power, and the paralyzed leg had about one third normal strength.

Both clinical measurements and teleoroentgenograms in another case (Case 60479) demonstrated that there was some shortening soon after onset, then the growth rate was essentially the same until about the age of thirteen, when the discrepancy increased, apparently owing to premature cessation of growth of the shorter leg. Measurement of teleoroentgenograms indicated that the shortening in this case was in both the femur and the tibia, but it may occur in the femur alone, in the femur and the tibia or in the tibia alone.

#### *Cause of Unequal Growth*

At one time a theory was proposed that the virus of poliomyelitis might directly affect one or more hypothetical growth centers in the central nervous system. No satisfactory evidence indicates that these growth centers exist, and the theory may be dismissed as extremely improbable.

The observed fact that unequal growth occurs only when there is unequal paralysis leads to the assumption that the relative amount of use of the two extremities is an important factor.

Another related factor is the circulatory status of the two extremities. Decreased circulation probably causes retardation, and increased circulation stimulation of growth of the involved extremity. Quantitative measurement of the circulatory status of the

extremities in poliomyelitis should prove to be a fruitful field for investigation.

#### *Equalization of Leg Length in the Adult*

The prevention and correction of discrepancies in leg length in poliomyelitis has engaged the interest of clinicians for many years. The methods of equalization of leg length available for adults are the use of a high sole, lengthening of the shorter limb and shortening of the longer limb. Adult discrepancies of less than  $\frac{3}{4}$  inch may, as a rule, be ignored. Occasionally, backache due to abnormal strain develops in these cases, requiring the use of a heel lift to equalize length.

Adults with moderate shortening ( $\frac{3}{4}$  to  $1\frac{1}{2}$  inches) usually require some shoe correction, whereas those with over  $1\frac{1}{2}$  inches of shortening almost invariably use a high sole to equalize length. The optimal amount of shoe correction depends upon a number of factors, which must be taken into consideration in each case. Complete equalization of length is rarely indicated, for the weaker leg, which is also the shorter one, is usually handled more easily if it is left slightly shorter. The clinician may estimate the amount of correction needed by placing blocks beneath the shorter leg as the patient stands barefoot. Sufficient lift is used to level the pelvis and to correct the list of the spine. The correction on the heel should be about  $\frac{1}{2}$  inch less, and the sole lift  $\frac{3}{4}$  to 1 inch less than the amount of lift necessary to correct the shortening completely.

#### *Leg Lengthening*

The first successful case of lengthening of the femur was reported in 1905 by Codivilla,<sup>9</sup> and additional cases were subsequently reported by Putu and Landini,<sup>10</sup> Abbott and Crego<sup>11</sup> and Compere.<sup>12</sup> But the operation is rather formidable and carries some risk of disaster from sepsis (osteomyelitis) and from delayed or absent union. The prolonged skeletal traction required is painful and necessitates several months of hospitalization. A full range of knee-joint motion after this operation is rarely obtained, and in a high percentage of cases, knee function is severely and permanently impaired. The operation of femoral lengthening was therefore soon abandoned.

Lower-leg lengthening (tibia and fibula) gradually supplanted femoral lengthening, and during the early 1930's enjoyed a considerable vogue. Abbott,<sup>11</sup> Wilson and Thompson<sup>14</sup> and others have used it successfully, most of the patients being children or young adults. Barr and Ober<sup>15</sup> reported a small series of cases in adults with good results. Lengthening of over 3 inches has been reported, but the average gain in length is 2 inches or less. This operation is subject to the same risks of sepsis and delayed union as femoral lengthening, and although knee-joint function is not appreciably affected, the ankle and foot are usually pulled into a deformed position (equinovarus), which requires operative

revision and stabilization of the foot in most cases. These and other problems make the procedure of leg lengthening one not to be embarked upon lightly. It is safe to say that the operation, once reasonably popular, is now rarely done.

### *Leg Shortening*

Shortening of the longer leg is the surgical alternative to leg lengthening in adults. Femoral shortening has been reported by several authors,<sup>14, 16-18</sup> and a number of variations in surgical technic have been proposed. The operation is not too difficult, the risk of sepsis and nonunion is less than that in leg lengthening, and the joint function is, as a rule, not impaired. The period of hospitalization and of disability is much less for femoral shortening than for leg lengthening. Femoral shortening in most clinics is now the operation of choice for equalization of adult leg length.

Shortening of the tibia and fibula is also a feasible method of equalization of leg length and has been performed in a small number of cases by Ober and by me. It is technically not so difficult as femoral shortening, and a leg cast only is required for post-operative immobilization, whereas femoral shortening requires a spica cast or suspension of the leg on a splint with the patient confined to bed. In 2 of my cases, there was marked postoperative swelling, with impairment of circulation of the foot, apparently owing to kinking of the blood vessels. Lumbar sympathetic novocain block and lumbar ganglionectomy may be of benefit if this complication occurs. The operation may prove to have advantages over femoral shortening.

Many patients and not a few surgeons are averse to major elective surgery on an extremity that is normal or nearly so. Though the procedure of leg shortening does not carry undue risk, it should be undertaken only after careful study of the problem by the surgeon and with the patient fully informed of the risks involved. Both the patient and the surgeon may accept the risk in the reasonable expectation of success. Freedom from a cumbersome, conspicuous, high sole is a goal worth striving for. The operation should be performed only if the weaker, shorter limb will be freed of all apparatus. If the patient must still wear a brace, little relative improvement is to be obtained by elimination of the high sole.

### *Equalization of Leg Length in the Growing Child*

The prevention of length discrepancy in the growing child has engaged the orthopedic surgeon's attention for many years, and today there is great interest in this problem. If a child has asymmetrical muscular weakness, what can be done to prevent or ameliorate the discrepancy in leg length that may be anticipated in such a case?

*Nonoperative measures.* So far as possible one should promote and maintain equal function in the

two legs. Full use of one limb and full immobilization of the other for prolonged periods should be avoided. In particular, prolonged plaster immobilization of the slower-growing extremity is harmful. The slower-growing limb should be dressed warmly and kept from chilling in cold weather, for it is logical to assume that there is an optimal temperature for growth of the epiphyseal plates.

*Operative measures.* The insertion of ivory pegs into or near the epiphyseal plates to stimulate growth was recommended and performed several decades ago without demonstrable beneficial effect. Similarly, juxtaepiphyseal drilling,<sup>19</sup> more plausible in theory, has proved disappointing on clinical trial and has been abandoned in most clinics.

Sympathectomy to stimulate growth was first proposed by Harris<sup>20, 21</sup>. If the operation is properly performed<sup>22</sup> the skin temperature of the affected limb is demonstrably raised, and the effect appears to be long lasting. In addition to the effect on growth, the cold, blue, lower extremity subject to excessive sweating, chilblains and ulcers is replaced by a warm, pink, dry lower extremity. The exact effect of sympathectomy on growth is difficult to assess in quantitative fashion. In 8 out of 9 cases in which sympathectomy was performed at the Massachusetts General Hospital, in an attempt to stimulate growth, the rate of growth of the affected limb kept pace with or actually exceeded that of the opposite limb. In only 1 of 4 cases has increased shortening occurred after sympathectomy. End-result studies on a larger series of cases are needed before final conclusions can be drawn, but this operation holds promise of being of real value. It is essentially without risk, hospitalization is short, and convalescence is rapid. It cannot be expected to be of much benefit if marked shortening has already occurred or if the operation is done after the age of twelve or thirteen. The young child with marked paralysis of one extremity and a nearly normal opposite extremity is a good candidate for this operation, particularly if the affected limb is cold and blue, perspires freely and is subject to chilblains.

Retardation of growth of the longer leg by operative arrest of growth of one or more epiphyseal plates (epiphyseal arrest, or epiphyseodesis) was first proposed by Phemister.<sup>23</sup> Several authors have reported series of cases in which the operation has been done and have discussed selection of cases, operative technic and end-results.<sup>19, 24, 25</sup> The epiphyseal plates most commonly fused are those near the knee joint—that is, those of the lower femur and the upper tibia and fibula. There is no doubt that the operation effectively retards growth. If the lower femoral epiphyseal plate contributes approximately 40 per cent and the upper tibial 25 per cent of the total leg length, fusion of these

two growth centers should retard further growth of the extremity by 65 per cent. But numerous difficulties arise in connection with this procedure. There is no accurate method of long-range prediction of the final discrepancy in leg length that would occur if no corrective measures were instituted. Until a satisfactory method of growth prediction is evolved, the age at which epiphyseal arrest should be done cannot be accurately estimated. White and Warner,<sup>25</sup> Gill and Abbott,<sup>6</sup> Straub, Thompson and Wilson<sup>24</sup> and Green and Anderson<sup>4</sup> have worked out methods of predicting the retarding effect of epiphyseal arrest on growth. The method of Green and Anderson has the virtue of simplicity, since the amount of retardation of growth to be obtained by epiphyseal arrest at any given skeletal age may be read directly from a chart. The operative technic of epiphyseal arrest consists in excising medial and lateral portions of the epiphyseal plate and replacing them with bone blocks, which extend into both the epiphysis and the diaphysis. An operative procedure that the authors consider satisfactory is described in detail. Not all surgeons have found the operation either easy to perform or uniformly successful in outcome. Deformities of the knee (valgus, varus and recurvatum) were noted in 6.5 per cent of cases reported by Green and Anderson<sup>4</sup> and in 11 per cent of those reported by Wilson and Thompson<sup>14</sup> and Regan and Chatterton.<sup>26</sup> Almost 10 per cent of the series of Green and Wilson required secondary operation because of deformity or lack of effective fusion of the epiphyseal plate or for arrest of the opposite side because of overcorrection.

Nevertheless, epiphyseal arrest is a method of proved success. It can be expected to equalize discrepancies in length of considerable magnitude. Careful consideration must be given to proper case selection. The correct age for operation and the epiphyses to be fused must be carefully determined. The operation must be meticulously performed. Attention to these factors will ensure that approximately 90 per cent of the patients will reach adult life with shortening of no clinical significance.

*Irradiation to retard longitudinal growth.* For a number of years Barr and his associates<sup>27, 28</sup> at the Massachusetts General Hospital have carried on experimental work on animals as a preliminary to the clinical use of irradiation. This work indicates conclusively that x-ray irradiation of the growing epiphyseal plates of the rat and the dog produces definite retardation in longitudinal growth. Single doses of 800 to 1200 r were effective, and the retardation was roughly proportional to the dosage employed. The maximal retardation in growth of an individual epiphysis was about 80 per cent, but the retarding effect was lessened by an overgrowth of adjacent, untreated epiphyses. The net maximal retarding effect on growth of an individual bone by treatment of one epiphysis was about 30 per cent.

Histologic examination revealed no evidence of damage to skin, subcutaneous tissues, muscle and bone. The articular cartilage, though normal to gross examination, showed mild but definite microscopical changes indicative of cellular damage. The clinical use of x-ray irradiation to prevent shortening or to equalize discrepancies in length already acquired must be considered to be in the experimental stage. It holds definite promise, however, and may prove to be a useful and effective method.

### SUMMARY

Normal growth is influenced by many hereditary and environmental factors, which determine the size and shape of limbs. It is extraordinary that symmetrical limbs of equal length are the rule and not the exception.

The causes of unequal growth of the legs, resulting in shortening, are discussed, with particular attention to poliomyelitis.

The exact incidence of leg shortening due to poliomyelitis is not known, but approximately a third of the patients with poliomyelitis treated in the Out-Patient Department of the Massachusetts General Hospital with onset before the age of sixteen developed marked inequality in leg length. The factors of importance in determining whether a patient will develop discrepancy in leg length include age at onset, sex and the amount and distribution of muscular weakness of the legs. There will be no shortening if the involvement is symmetrical. The greatest shortening occurs in young patients with one normal and one severely paralyzed limb.

Inspection of growth curves of individual cases suggests that the growth retardation is not constant. The maximum retarding effect appears in some cases to occur late in the growing period. Premature cessation of growth associated with epiphyseal closure on the paralyzed side may explain late occurrence of severe discrepancies. Exact prediction of the amount of shortening to be expected in a given case is not yet possible. The possible causes of unequal growth in poliomyelitis include changes in circulation and disuse of the extremity.

Operative correction of adult discrepancy in length is possible by leg-lengthening or leg-shortening procedures, the latter appear to be preferable.

In the growing child epiphyseal arrest offers a method of equalization that in properly selected cases is very effective. Careful attention must be given to the proper age for intervention and to the operative technic.

Sympathectomy as a procedure to maintain equality in leg length is still *sub judice*, but it appears to be of value if done early enough.

Every growing child with poliomyelitis should be under the regular supervision of an orthopedic surgeon who is thoroughly familiar with the problem of unequal growth. Regular measurement of the

leg length, clinically and by x-ray examination, will allow early detection of shortening. The surgeon by suitable selection of operative methods and by promotion of normal function in the affected extremity will be able to prevent much of the shortening that would otherwise occur. The unsightly cork or wooden high sole should become a much less familiar sight. Eventually the time may come when no child will need to face adult life with that handicap.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 34211

#### PRESENTATION OF CASE

A fifty-six-year-old engineer was admitted to the hospital because of pain in the right side and difficulty in breathing.

Approximately six months before admission the patient developed a cough productive of "white mucus," but had no other symptoms. Seven weeks before admission he awoke one morning with a severe pain in the right lower chest, which was made worse by breathing. Records from the hospital in which he was treated stated that there were physical and x-ray findings of a pulmonary infarct. He was given penicillin and dicumarol

During the hospital stay he became violent and developed delusions of persecution. After three weeks of hospitalization he was discharged but was never free of chest pain. Later, this became worse and was aggravated by breathing. Two days before entrance to this hospital an x-ray film taken at another hospital was reported as showing "a large abscess cavity in the right subdiaphragmatic region and a right-sided pleuritis." He lost approximately 35 pounds in the course of the illness.

The patient had had a "double coronary" seventeen months before admission. He had had occasional ankle edema and slight exertional dyspnea since then.

Physical examination revealed a man with somewhat grandiose ideas and with some difficulty in thinking of words. The chest was emphysematous with expansion limited by pain. There was dullness over the lower third of the right chest posteriorly. The right leaf of the diaphragm was elevated and limited in excursion. Breath sounds and vocal fremitus were diminished over the right lower chest. A friction rub was audible posteriorly near the right base. The liver edge was palpable three fingerbreadths below the costal margin and was tender.

The temperature was 99°F, the pulse 120, and the blood pressure 110 systolic, 80 diastolic.

Examination of the blood disclosed a hemoglobin of 12.2 gm and a white-cell count of 16,700, with 89 per cent neutrophils. The urinary sediment contained a rare white cell. The sputum was negative for acid-fast organisms.

An x-ray film showed questionable fluid over the lower half of the right chest. The middle lobe was collapsed. There was a fluid level with an air space above it at the right base. The right leaf of the diaphragm could not be identified, since it did not move with respiration. The left lung field was clear. An electrocardiogram showed low voltages and probable right-axis deviation. In addition, in the chest leads the S waves were prominent, and the R waves small to absent.

The patient was prepared for a thoracotomy on the second hospital day. Quinidine (0.15 gm) was given one hour before operation. A short time after the intratracheal tube had been inserted the patient stopped breathing, and no pulse could be obtained. Attempts at resuscitation were unsuccessful.

#### DIFFERENTIAL DIAGNOSIS

DR F DENNETTE ADAMS: One must consider the entire gamut of subacute and chronic pulmonary diseases: tuberculosis, abscess, bronchiectasis, foreign body, actinomycosis and others. However, the evidence in this case seems typical, if one can say anything in medicine is typical, of bronchiogenic carcinoma. The illness started with cough, virtually nonproductive, for four weeks. There were no other symptoms except quite rapid loss of weight. Then an acute episode occurred—fever and pain in the chest. The record from the other hospital states that the patient had typical signs and x-ray findings of pulmonary infarction. One hesitates to be critical, and yet it should be pointed out that this is a broad statement.

Pulmonary embolism presupposes thrombophlebitis or phlebothrombosis. If the patient was up and around, phlebothrombosis would not be likely, if he had thrombophlebitis, he would have in all likelihood signs in his legs. So there is very little ground for presupposing trouble in the veins unless one wishes to assume that it was there because of the presence of a malignant lesion elsewhere. In my opinion, one cannot say that either the physical or x-ray signs were necessarily typical of pulmonary infarction. Similar signs may occur in collapse and in pneumonia. Furthermore, when the signs appear with pulmonary embolus in the lungs they have to be due to a fairly large embolus, and in such a case one would expect at the onset some signs of temporary insult to the circulation. This patient apparently had no such episode. I am much more inclined to believe that the trouble was infection: pneumonia or, if my original assumption is correct, more probably secondary infection behind complete obstruction of a bronchus. Another

good reason for believing that this was not a pulmonary infarction is the fact that the pain continued, the patient with pulmonary infarction recovers rapidly unless more emboli form.

This man continued to be sick, to have pain and to lose weight. He came into the hospital with grandiose ideas and difficulty in thinking of words. We shall come back to this in a moment. The signs in the chest on admission to this hospital could have been due to almost any form of pulmonary disease: low-grade infection, thickened pleura, fibrosis or collapse or a combination of these. The statement that the right leaf of the diaphragm was elevated cannot be made if other recorded physical signs were correct. With dullness and diminished respiratory sounds the diaphragmatic movements could not be determined accurately. The patient still had a friction rub. We can assume that he had it all along because of the pleural type of pain. The white-cell count indicated a suppurative form of infection, and this was borne out by the x-ray film, which showed a pulmonary abscess. This could be secondary to pneumonia, bronchial obstruction from foreign body, tumor or other cause or to infarct.

My belief is that in a man of fifty-six with this history and the disease taking the course described, one is justified in making almost a flat-footed diagnosis of bronchiogenic carcinoma with obstruction and secondary infection.

Will Dr Wyman demonstrate and discuss the films for me?

DR STANLEY M WYMAN: There seems to be definite fluid along the lateral margin of the right chest. The right leaf of the diaphragm cannot be identified laterally, but there is a suggestion of the diaphragm medially, and a large cavity containing air and fluid. A definite fluid level is seen in the midlower portion of the lower lung field, which lies posteriorly in the lateral view. The right lower lobe appears to be diffusely consolidated and perhaps slightly decreased in size. I cannot identify the collapse of the middle lobe described.

DR ADAMS: Is the lung pulled over a little?

DR WYMAN: It does not seem so to me. The chest is rotated slightly. The spine in its midportion lies here to the left so that this appearance might be due to the rotation of the patient on the film. I can identify the left main bronchus fairly well. The right main bronchus I can follow only down to about 3 cm beyond the bifurcation. I cannot make out a definite mass, but there is a suggestion of some hazy density overlying this portion of the hilus, with a poorly defined lateral border.

DR ADAMS: I am still going to stick to the diagnosis already made. The best bet in a man of fifty-six years, who has cough for several months, then develops an abscess and meanwhile loses weight and goes downhill, is a malignant lesion of a bronchus, with obstruction and secondary infection.

As I read over this record, I wondered about the haste in operating. The patient came in one day and was prepared for operation on the next. He was not bronchoscoped. Little attention seems to have been paid to what appears to have been a significant factor when the man was in another hospital several weeks previously he was paranoid, and while in this hospital he had obvious personality changes. The degree of fever is hardly sufficient to account for so much personality change. No studies were done to try to determine its cause. One cannot exclude a psychosis unrelated to the rest of the picture, and yet that seems no more than tenable. The patient could have had general paresis, but we have no evidence at all. He could have had — and this merits particular emphasis — a drug psychosis, a disturbance often overlooked because not thought of. He had pain for a long time. We do not know what medication he was getting. He may have been filling himself up with bromides or barbiturates. I have recently seen 2 cases of bromide poisoning resembling this picture. The other possibility, and the one that seems to me most likely, is a metastatic lesion in the head, either carcinoma or abscess. One cannot distinguish between the two, but on general principles, if my basic diagnosis is correct, metastatic cancer seems more likely than abscess.

What was the cause of death? The patient was known to have had a coronary infarction. The electrocardiogram showed low voltage, suggesting a poor myocardium or, less likely, pericardial disease, perhaps spread of the tumor into the pericardium. The changes in the R and S waves suggest the possibility of residua of old coronary-artery disease. One cannot state that the sudden death was not due to heart failure. Certainly, the small dose of quinidine cannot be held responsible. On the other hand, we must remember that the patient had been subjected to some manipulation while the intratracheal tube was being inserted, and I think that he may have died of a pressure cone although this is really not much more than a guess. Since a diagnosis must be ventured, I am going to commit myself to carcinoma of the bronchus with secondary infection of the lung due to bronchial obstruction, metastatic carcinoma of the brain and death from a pressure cone.

DR DONALD S. KING Are you sure that the process is not below the diaphragm, Dr. Wyman?

DR WYMAN No, I am not sure by any means. I think that I can outline the right leaf of the diaphragm medially and also in the lateral view anteriorly. I cannot be sure but I think that it is above the diaphragm.

DR JOHN QUINCY Do you think that there is some emphysema on the left?

DR WYMAN The films are overexposed to bring out the details in the right lung, making accurate statement about the left lung difficult. However, there is some emphysema on the right side.

DR ADAMS That could be explained on the basis of compensation.

DR WYMAN Yes, there is a little compensatory emphysema in the upper lobe on the right side.

DR ADAMS The patient had an overdistended lung base. We know that he used that lung more for the air that he needed.

DR WYMAN It is not a process of long standing, however, and the anteroposterior diameter of the chest is not significantly increased.

DR CARROLL C. MILLER I saw this patient in another hospital before he was admitted to the Baker Memorial. At first sight he was a very sick man and obviously not getting better. The local physician and I could not make a definite diagnosis. X-ray films taken in the other hospital were perhaps more equivocal than ours are in determining the location of the diaphragm, and we did not know whether the abscess cavity, this air-filled pocket with fluid in it, was below or above the diaphragm. The patient was mildly confused in his thought processes, and it was difficult to get a clear-cut, consecutive story from him. The history showed no evidence of drug toxicity. He had been followed for several months in a hospital in the Midwest and later at this local hospital. It was thought that drugs did not enter into the picture. He had had a definite change of personality and at one time had threatened his wife.

DR ADAMS Are you sure that was not routine?

DR MILLER That was a definite change. I had him admitted to the Baker Memorial, and because of improvement in his mental status at the time, this did not seem to be a problem. Because of the fact that he was running a spiking temperature Dr. Richard H. Sweet decided to drain the area as soon as possible. We had entertained the possibility that the process was a subdiaphragmatic abscess, and it was rather difficult to make sure that he had not had a ruptured ulcer because he had had vague upper abdominal fullness within the past year. That added to the confusion in trying to determine whether the lesion was above or below the diaphragm. The physical findings on admission here were the same as those at the other hospital — diminished breath sounds with rales at the right base.

In reference to your remark about confinement to bed, he was immobilized for a considerable period in a hospital in the Midwest during the episode of coronary-artery disease.

DR ADAMS That had been eighteen months before, however.

DR MILLER Yes, a long time before. The possibility of infarcts with subsequent breakdown and abscess formation within the lung occurred to all of us. The picture did not appear like a clear-cut lung abscess to us. There was no foul-smelling sputum during the course of the disease, and the cough seemed not to be a major problem. It was not

the typical cough that accompanies carcinoma of the bronchus, which is more commonly an irritative one. Of course we had had in the back of our minds carcinoma of the lung, not infrequently we see such cases without typical symptoms.

A word about the anesthesia—it was entirely uneventful. During the induction of anesthesia the patient was quite dry, and there was no appreciable amount of struggling. He simply stopped breathing just as he was to be taken into the operating room and could not be revived.

#### CLINICAL DIAGNOSES

Coronary occlusion  
Subdiaphragmatic abscess?

#### DR ADAMS'S DIAGNOSES

Bronchiogenic carcinoma, with metastasis to brain  
Secondary lung abscess  
Pressure cone

#### ANATOMICAL DIAGNOSES

*Empyema, right pleural cavity*  
Coronary sclerosis, with occlusion  
Infarct of heart  
Emphysema, moderate

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Autopsy showed that the cavity was above the diaphragm and was entirely within the pleural cavity, a large encapsulated empyema. We were not able to identify any intrapulmonary lung abscess. There remained the possibility, of course, that there had been a small intrapulmonary abscess that had ruptured into the pleura and had been the source of the empyema. The old coronary-artery disease was sufficient to have caused complete occlusion of the descending branches of the left coronary artery and a very large area of infarction at the apex of the left ventricle, running halfway up the interventricular septum. This was covered by a thick partially organized thrombus. There was no evidence of cancer, and no lesion could be found in the brain—abscess, infarct or tumor.

DR ADAMS Why did the patient die?

DR MALLORY I cannot explain the mechanism. He had the type of heart with which a patient could die instantly.

## CASE 34212

### PRESENTATION OF CASE

A fifty-three-year-old hospital employee was admitted to the hospital complaining of nausea, vomiting and diarrhea.

His employment at the hospital began two months before admission. A routine examination was negative. The heart and lungs were within normal limits on physical and x-ray examination. The blood pressure was 140 systolic, 88 diastolic. A routine urine examination demonstrated an acid urine, with a specific gravity of 1.018 and the absence of sugar and albumin. A microscopical examination of the urinary sediment was not done. Two weeks before admission the patient began to feel "logy," vaguely sore between the shoulder blades and chilly (without frank chills). On the next day he lost his appetite and noticed that his throat was sore. He became nauseated, vomited all food and liquids ingested, including water, and began to have watery bowel movements, up to four or five a day. These complaints continued up to admission. One week before admission dyspnea on climbing one flight of stairs appeared. He had never had any dyspnea previously. There was no orthopnea. He had a slight tickling cough, productive of small amounts of whitish sputum. A week before admission he blew a clot of blood from his nose, but he insisted that he had not actually coughed up any blood. On the day before admission the nasopharynx was injected, general physical examination was otherwise not remarkable, and he was afebrile. A chest film demonstrated cardiac enlargement, with pulmonary congestion and a small right pleural effusion (Fig 1).

The only previous illness he could recall was an attack of "asthma" about six years before entry, which subsided without treatment.

Physical examination revealed that the patient was not acutely ill, but was somewhat pale, the tongue was dry, and the throat was beefy and a little edematous. The superficial veins of the neck were distended 1 or 2 cm above the clavicles in the semierect position. A few, moist, inspiratory rales were present at both lung bases, and there was some dullness over the right base. The heart was slightly enlarged to percussion. No murmurs were present. The sounds were distant and of poor quality, but no gallop rhythm was heard. The liver

edge was percussed 3 cm below the right costal margin. There was slight tenderness to percussion in both costovertebral angles, more on the right than on the left. The prostate was very slightly enlarged. There was slight pitting edema over the ankles. No calf tenderness was present.

The blood pressure was 185 systolic, 95 diastolic.

Examination of the blood disclosed a red-cell count of 3,200,000, with a hemoglobin of 11 gm per 100 cc, and a white-cell count of 9900, with 86 per cent neutrophils. The specific gravity of the urine varied between 1.015 and 1.022, and there was a +++ test for albumin. Repeated examinations of the urinary sediment demonstrated between 5 and 15 red cells and between 20 and 50 white cells per high-power field. Many hyaline, granular and red-cell casts were found. The fasting blood sugar was 113 mg., the nonprotein nitrogen 100 mg., and the total protein 6.6 gm per 100 cc. The carbon dioxide was 17.7 milliequiv., and the chloride 104 milliequiv per liter.

Three hours after admission to the Emergency Ward and thirty minutes after arriving on the hospital ward the clinical condition changed dramatically, and severe, acute, pulmonary edema appeared. Therapy included morphine, oxygen by mask, intravenous cedilanid and amioephyllin. An initial response to this treatment was favorable, but a picture of pulmonary edema continued. On the second hospital day there was distinct mental confusion, with mumbling and lapses of memory. On the next day the nonprotein nitrogen was 125 mg., the calcium 8.2 mg., and the phosphorus 7.5 mg per 100 cc. The chloride was 110 milliequiv., and the carbon dioxide 18.9 milliequiv per liter. The patient died that day.

#### DIFFERENTIAL DIAGNOSIS

DR BRIANT L. DECKER: May we see the x-ray films? Have you the old films?

DR STANLEY M. WYMAN: No, they are not available. In this recent series of films the heart shadow cannot be adequately outlined, but it seems to extend farther to the right and left than is normal. The heart, although it cannot be well seen, is probably enlarged. There is a definite pleural effusion on the right obscuring the costophrenic angle. The diaphragm is elevated, with localized effusion in the minor septum between the right

upper and the middle lobes. There is probably some fluid on the left, although that cannot be stated with certainty. The pulmonary vascular shadows of both hili are definitely increased. This increased prominence extends fairly well out into both lung fields peripherally. One cannot see any definite intrinsic localized pulmonary disease. There



FIGURE 1

is nothing specific that one can say about the configuration of the heart.

DR DECKER: Do you believe that the hili are consistent with congestive failure?

DR WYMAN: Entirely consistent with congested arteries, but the possibility of nodes in one or both hili cannot be excluded. This might be determined by fluoroscopy, one cannot exclude nodes from the films alone.

DR DECKER: In summary, we have the history of a fifty-three-year-old man whose only known previous illness was an attack of asthma six years before admission, the details of which are not given. He was in apparently good health until two months before admission except for the possibility of slight hypertension. For two weeks before admission he had symptoms of acute infection localized in the pharynx, but he also had gastrointestinal symptoms. One week after the onset of this infection he de-



veloped symptoms of congestive failure, and on admission to the hospital, examination showed acute pharyngitis, fairly marked hypertension and signs of both right-sided and left-sided cardiac failure. Laboratory tests revealed a slight normochromic anemia, a high normal white-cell count, with a fairly marked neutrophilic reaction, a urine typical of, or rather consistent with, acute glomerulonephritis and blood chemical findings indicating a nonprotein nitrogen retention and moderate acidosis. Although the patient did not appear very ill on admission, he shortly afterward developed severe acute pulmonary edema, which responded poorly to treatment. Within twenty-four hours he developed mental confusion and within forty-eight hours died, I believe of congestive failure.

Of the possible explanations of the history the first condition that comes to mind is acute glomerulonephritis. The patient was older than is usual with that condition, but there have been at least 2 cases of acute glomerulonephritis in elderly patients reported here in the past year. I must assume that the onset of the nephritis was coincident with or very shortly followed the acute throat infection. This is not very usual. It is possible and even probable that the onset of the initial infection that caused the acute glomerulonephritis was unnoticed, and that the symptoms that were evident two weeks before admission — nausea and vomiting, particularly — indicated the onset of renal failure and nitrogen retention. It is not unusual for a patient with acute glomerulonephritis to go into uremia as quickly as this patient apparently did, but in a small percentage of these cases that happens. More often the patient develops hypertensive encephalopathy, with marked cerebral symptoms and convulsions. These symptoms are not dependent on a high nonprotein nitrogen. In this case, however, the nonprotein nitrogen was considerably elevated and rising, and there was a low serum calcium, an elevated phosphorus and a decreased carbon dioxide — all characteristic of uremia. The cerebral symptoms were only moderate, and there were no convulsions.

An acute flare-up of chronic pyelonephritis or an initial onset of acute pyelonephritis seems unlikely to me because of the absence of typical symptoms — chills, a febrile course and so forth — of characteristic urinary findings. I believe that the finding of casts, particularly the red-cell casts,

is against pyelonephritis. For similar reasons bacteremia with an acute focal nephritis does not seem tenable. However, another condition that might well explain the whole picture is periarteritis nodosa. This usually affects younger persons but may occur at any age. It is usually of weeks' duration, runs a febrile course and is almost invariably associated with, or follows, an acute infectious process. The febrile course was not evident in the case under consideration, but the period of observation was brief. Renal lesions are present in a high percentage of these cases, — about 80 per cent, — and frequently these are suggestive of acute glomerulonephritis, with accompanying renal failure. Cardiac involvement is likewise very frequent. The symptoms of periarteritis nodosa may be so varied that it is a very convenient condition to mention in these discussions. It is rather difficult for me to decide between these two conditions, but on the basis of probabilities it is my opinion that this man had acute glomerulonephritis. It may have been associated with periarteritis nodosa, but that is my second choice. I believe that he died of congestive failure and had uremia.

DR LINCOLN CLARK. I can add a few details. During the last day the patient developed a paranoid psychosis. He believed that we were trying to poison him, refused medication and became belligerent and combative. I examined him but could find no change from the previous day. The nurse called me because he had refused to take penicillin. He was wildly thrashing around and snatched the stethoscope from me. Five minutes later he was dead. The examination of the chest, so far as it could be accomplished, revealed the clinical findings of pulmonary edema with markedly diminished respiratory exchange. The psychotic episode was probably the preliminary phase to the pulmonary edema of which he died.

DR TRACY B MALLORY. Does no one want to suggest a lower-nephron nephrosis? Patients with that condition commonly die of acute pulmonary edema, and it is statistically becoming more frequent than glomerulonephritis. There are two points in the history that are strongly against it. One is the specific gravity of 1.022, which would be very much higher than one would expect, the other is the red-cell casts.

DR WYMAN. From the x-ray point of view pulmonary edema, vascular congestion and pleural

effusion are all present. This may be associated with nephritis and might be the result of it. One would have to suppose that the patient had pre-existing or co-existing heart disease because of the degree of cardiac enlargement.

DR MALLORY That film was taken the day before the clinical evidence of pulmonary edema developed.

DR WYMAN Yes, he already had x-ray evidence of edema at that time.

DR DECKER I considered the possibility that the attack of asthma six years previously was really an attack of acute pulmonary edema, indicating a damaged heart then, and that this superimposed elevation of blood pressure, uremia and so forth, was enough to produce this picture. That is one reason why I wanted to see the old x-ray films to determine if at that time the heart was borderline in size.

#### CLINICAL DIAGNOSES

Acute pulmonary edema

Uremia due to nephritis,

unknown cause, and to

cardiac insufficiency of two weeks' duration

#### DR DECKER'S DIAGNOSES

Acute glomerulonephritis

Uremia

Congestive failure

#### ANATOMICAL DIAGNOSES

*Acute glomerulonephritis*

*Chronic vascular nephritis, slight.*

*Acute pulmonary edema.*

Hypertrophy and dilatation of the heart, hypertensive type

Hydrothorax, bilateral

#### PATHOLOGICAL DISCUSSION

DR MALLORY At autopsy we found enlargement of the heart and the kidneys. The heart weighed 460 gm. The coronary arteries were in very good condition, and there were no valvular lesions so that we are forced to assume that there had been a hypertensive heart disease of considerable standing.

The kidneys were very much enlarged, they weighed 500 gm. The capsule stripped with difficulty, leaving a pitted surface that suggested underlying renal disease of long standing, but the microscopical sections showed an extremely acute glomerulonephritis. I think it was superimposed on a slight chronic vascular lesion, which probably had been present for many years. The fresh episode is very characteristic of acute glomerulonephritis, and could not possibly be confused with the so-called "malignant phase" of vascular nephritis. The fatal episode of acute pulmonary edema is not the usual mode of exit for these cases with a non-protein nitrogen still as low as 120 mg per 100 cc. We saw death from pulmonary edema very frequently in crush and shock kidneys during the war, but in most of those cases the picture was complicated by a great deal of parenteral fluid, which was not given to this man. Consequently, the pulmonary edema in this case was not brought on by treatment. I am inclined to attribute it to acute heart failure rather than to renal failure.

DR ALFRED KRANES What was the urinary output during observation?

DR MALLORY The patient was in the hospital for such a short time that it is not known.

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## "A PATTERN FOR CHILD HEALTH"

THE country-wide study of child-health services, launched in March, 1946, by the American Academy of Pediatrics at the successful conclusion of the pilot study in North Carolina, has been finished. Detailed state by state reports and recommendations are being prepared, the national report will be issued this summer.

The findings of this million-dollar study, financed by the Academy, the federal Government, various foundations, business firms and state organizations were entirely predictable although never before specifically stated. Adequate pediatric care, according to the preliminary reports, does not reach the people, effectively distributed. Isolation from the

potential benefits of good medical practice prevails for individuals, for families, for communities and for economic levels of society, the result of geographic and economic factors and of ignorance.

Erratic failures to balance supply and demand persist. There are not enough doctors in practice where doctors are most needed, and too many flock to those communities or sections where better facilities for practice may exist, or where the economic level of the population is higher. In some communities the doctors are available but hospital beds are lacking, in others the beds are available but the doctors are absent. It may be said that in general the pediatric training of physicians is inadequate. Unavailable medical care in the country and failure to utilize available medical care in the city are still responsible for many child deaths. In various aspects relating to health promotion we have even fallen behind some of our progressive neighbors such as Canada and the Scandinavian countries.

Once a diagnosis has been established and accepted the way is open for any possible therapy to be applied, and in this instance the disease is definitely curable. A network of medical services must be developed to cover every community, with hospitals, clinics, health services and physicians. The services of the metropolitan centers must be made to flow out to the rural hospitals. The training of young physicians must be improved to the point that all those in general practice, as well as the pediatricians themselves, will be equipped to give good child care.

The American Academy of Pediatrics has done a splendid piece of work in carrying through this ambitious program of fact-finding. Its business and that of all associated agencies will now be to work toward the proper application of the obvious remedies.

## FOUR HUNDRED AND THIRTY YEARS AGO

WE ARE so frequently impressed by the recent advances in scientific medicine, so pleased that we can rightly speak of milligrams and correctly determine the hemoglobin to a fraction of a percent — by machine let it be said — that we are prone to forget that our forebears, without so much as a

hlet or Technicon, laid the firm, substantial foundations on which we build today. Lakin's\* Harveian Oration of 1947 recalls our debt to mind.

Our own Association of American Physicians, of which we are justly proud, was founded in 1886 by such men as "Popsy" Welch and Dr. Councilman, known to all as "Councv." Such men as these, the founders and benefactors of our Association, have rightly earned the admiration and respect that is their due.

The British counterpart of this society, its father and mother so to speak, was the Royal College of Physicians founded nearly four hundred years earlier — in 1518 to be exact.

"In the year 1345 King Edward the third had allowed a pension of sixpence a day to Coursus de Gangland, an apothecary of London, for his attendance during his illness. Yet during the fourteenth and fifteenth centuries medical knowledge was at a very low ebb, and "The Peterhouse chained library of 1418 held but thirteen volumes of medicine," among which was the notable work of "Richard of Wendover (ob. 1252), canon of St. Paul's, the compiler of an encyclopedic treatise covering the entire field of medicine. "The one fellow of Cambridge allowed by statute to adopt the medical art was pursuing in 1418 the regular university course, he had borrowed Macer, *De Virtutibus herbarum* and the prescribed texts of Johannicus and of Isaac." When we recall that Johannicus was none other than Honein ibn Ishaq el 'Ibadi, that he died in the year of our Lord 873, and that "Isaac fuit arabs nacione" we realize that medicine then was surely in a sorry state.

Yet only one hundred years later, during the reign of Henry the Eighth — he of the elastic conscience — there was founded the Royal College of Physicians by Thomas Linacre, the Greek and Latin scholar who is said to have introduced the damask rose into England not long before he died in 1525.

There is no direct, unbroken line by which we may connect the medical practice of the ancients with that of the modern day. But it seems certain that during the Dark Ages Arabic medicine was supreme and that the most important results of the revival of learning in the fifteenth and sixteenth centuries

were the accurate translations from Greek into Latin of the great masters such as Hippocrates and Galen. Among the very foremost of these translators was Thomas Linacre, founder and benefactor of the Royal College. The revival of Hippocratic and Galenic medicine did not immediately produce any important reform in practical medicine, but the great outbreak in England of the "sweating sickness," described so well by John Kaye or Cains, a successor of Linacre, and the appearance of syphilis, seemingly unknown to the Greeks, made it clear that the works of Galen did not contain all that could be known of medicine. Thus were physicians of that day urged on to make their own observations and to a keener attention to the natural history of disease. As early as 1649 the hitherto undescribed rickets was carefully studied by Arnold de Boot, a practitioner in Ireland. From this point it is but a short step to Thomas Sydenham and thence to the great systemizers of medicine — Cullen and Brown. Medical knowledge seemed to wane at the end of that century but received new life from Auenbrugger and Laennec and from that time on with such minor alarms and excursions as the expressed belief of Hahnemann (1753-1844) that "Seven-eighths of all chronic diseases are produced by the itch driven inwards," progress in medicine has been steady until, today, we can speak of millimoles and the MCHC — whatever that may be.

Yet when all is said let us not forget the founders and benefactors of the Royal College, for they and their peers started us on our journey into the Golden Age of medicine from the Dark Ages when doctors were but pompous charlatans and when "If a poor man speke a word he shal be foul affronted."

## HYGEIA VERSUS PANACEA

As a reminder that the rehabilitation clinic is not a new idea, Miss Hazel Newton, general manager of The Community Workshops, has written a comprehensive letter that is published elsewhere in this issue of the *Journal*. War, with its hideous casualty lists, has swelled the ranks of the handicapped to a point where publicity is being focussed on their needs, the Community Workshops, in a very unassuming way, has been operating in the field of rehabilitation for over seventy years.

\*Lakin, C. E. Our founders and benefactors. *Brit. M. J.* 2:185-188 1946.

## NOTICES

## ANNOUNCEMENT

Dr James J O'Leary, Jr, announces the opening of his office at 97 Lincoln Street, Framingham, for the practice of surgery

## NEW ENGLAND DIABETES ASSOCIATION

The second annual meeting of the New England Diabetes Association will be held at the New England Deaconess Hospital, Boston, on Monday, May 24, from 4 00 to 5 30 p m

## PROGRAM

## Brief Business Session

Clinical Demonstrations Illustrating the Treatment of Diabetes at the New England Deaconess Hospital

Transmetatarsal Amputation — Immediate and Remote Results

Diabetic Coma — 91 Successive Cases Without a Death, With Credit Due to Family Physician

Potassium Deficiency

Demonstration — Pregnant Diabetic Patients and Their Treatment

The Victory Medal for Diabetes of Twenty-Five Years' Duration With Onset Under Twenty-Five Years of Age With Freedom from Degenerative Vascular Lesions

Uric Acid Diabetes

Essentials of Treatment of Diabetes Today

# NEW ENGLAND ALUMNI OF BALTIMORE MEDICAL COLLEGE, COLLEGE OF PHYSICIANS AND SURGEONS AND UNIVERSITY OF MARYLAND MEDICAL SCHOOL

The annual luncheon meeting of the New England alumni of Baltimore Medical College, College of Physicians and Surgeons and University of Maryland Medical School, will be held at the University Club, 40 Trinity Place, Boston, on May 26, at 12 30 p m. The section meetings and exhibits of the three-day annual meeting of the Massachusetts Medical Society at the Hotel Statler, beginning on May 25, will be open to visiting alumni. Reservations should be made before May 17 to the secretary-treasurer, Dr Charles E Gill, 184 North Street, Pittsfield, Massachusetts.

## NEW ENGLAND HEALTH INSTITUTE

The 1948 New England Health Institute will be held at the University of Massachusetts campus at Amherst on June 16, 17 and 18. Programs have been mailed to five thousand local and state health-department workers in the six New England states.

Panel discussions on advances in local health services, chronic illness and health needs of children will be supplemented by the varied topics on the five section meetings arranged for June 17 by the Massachusetts Public Health Association.

At special dinner meetings on June 16 and 17 addresses by Dr Leonard A Scheele, surgeon-general of the United States Public Health Service, and John H Crider, editor-in-chief of the *Boston Herald*, will be presented.

## NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, Boston, on Tuesday,

June 8, at 8 p m. A scientific program will be presented by the Rhode Island Hospital group.

## PROGRAM

Fluid Therapy Russel O Bowman, Ph D

Anesthesia for Hip-Nailing E F Neves, M D, and Margaret Iszard, M D

Some Considerations of Endotracheal Anesthesia Clement S Dwyer, M D, and Sanford Kronenberg, M D

Physicians and medical students are invited to attend

## NATIONAL CONFERENCE OF COUNTY MEDICAL SOCIETY OFFICERS

The third National Conference of County Medical Society Officers will be held at the Palmer House, Chicago, on June 20 from 10 a m to 4 p m.

Although the program is directed primarily to officers of county medical societies, any member of the American Medical Association is welcome to attend and participate in the discussion.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING

## THURSDAY, MAY 27

## FRIDAY, MAY 28

\*9 00-10 00 a m Some Actions of Folic Acid Conjugates and Antagonists on Malignant Tumors Dr Sidney Farber Joseph H Pratt Diagnostic Hospital

\*10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital

## TUESDAY, JUNE 1

\*12 00 m X-ray Conference Margaret Jewett Hall, Mt Auburn Hospital, Cambridge

\*12 15-1 15 p m Clinicorontgenological Conference Peter Bent Brigham Hospital

\*1 30-2 30 p m Pediatric Rounds Burnham Memorial Hospital for Children, Massachusetts General Hospital

## WEDNESDAY, JUNE 2

\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital

\*2 00-3 00 p m Combined Clinic by the Medical, Surgical and Orthopedic Services Amphitheater Children's Hospital

\*Open to the medical profession

MAY 20-25 American Board of Ophthalmology Page 170 issue of January 29

MAY 23-28 American Physiotherapy Association Page 543, issue of April 8

MAY 24 New England Diabetes Association Notice above.

MAY 24 New England Heart Association Page 722, issue of May 13

MAY 24-26 American Gynecological Society Page 543, issue of April 8.

MAY 24-27 Massachusetts Medical Society Annual Meeting Hotel Statler, Boston

MAY 25-27 Massachusetts Physicians' Art Association Page 722, issue of May 13

MAY 26 Massachusetts Medico-Legal Society Page 678, issue of May 6

MAY 26 New England Alumni of Baltimore Medical College College of Physicians and Surgeons and University of Maryland Medical School Notice above.

MAY 27-29 American Surgical Association Page 455, issue of March 25

JUNE 2 Children's Hospital Alumni Association Page 648 issue of April 29

JUNE 3-6 American Orthopaedic Association Page 614, issue of May 6.

JUNE 7-10 National Gastroenterological Association Page 455 issue of March 25

JUNE 8 New England Society of Anesthesiologists Notice above

JUNE 11 Harvard Medical School Class of 1898 Page 722, issue of May 13

JUNE 14-16 American Neurological Association Page 582, issue of April 15

(Notices concluded on page xiv)

## NOTICES (Concluded from page 754)

- June 16-18 New England Health Institute. Page 754  
 June 17-20 American College of Chest Physicians. Page 455 Issue of March 25  
 June 20. American College of Radiology. Page 722 Issue of May 11  
 June 20. National Conference of County Medical Society Officers. Page 754  
 June 20 and 21. American Radium Society. Page 543 Issue of April 8  
 June 21 and 22. American Society for the Study of Sterility. Page 581 Issue of March 11  
 June 23. University of Pennsylvania Medical Alumni Society. Page 678, Issue of May 6  
 June 25 and 26. Christian Medical Society. Page 492 Issue of April 1  
 June 28-30. American Academy of Pediatrics. Hotel Schroed Milwaukee Wisconsin  
 July 6-24. Students International Clinical Congress. Page 455 Issue of March 25  
 July 12-17. First International Poliomyelitis Conference. Page 36 Issue of January 1  
 August 11-21. International Congress on Mental Health. Page 344 Issue of March 4  
 August 21-26. International Society of Hematology. Page 419 Issue of March 18  
 August 26-28. American Association of Blood Banks. Page 420 Issue of March 18  
 September 7-11. American Congress of Physical Medicine. Page 582, Issue of April 15  
 September 13-15. American Academy of Pediatrics. Olympic Hotel Seattle, Washington.  
 September 20-23. American Hospital Association. Page 310 Issue of February 26  
 September 29. Mississippi Valley Medical Editors Association. Page 170, Issue of January 29  
 October 6-9. American Board of Ophthalmology. Page 170 Issue of January 29  
 November 1-3. American Clinical and Climatological Association. Page 582 Issue of April 15  
 November 8-12. American Public Health Association. Page 420 Issue of March 18  
 November 10-13. Association of Military Surgeons of the United States. Page 722, Issue of May 13  
 November 20-23. American Academy of Pediatrics. Annual Meeting Calhoun Haddon Hall Hotel, Atlantic City, New Jersey  
 December 7-9. Southern Surgical Association. Annual Meeting. Page 543 Issue of April 8.

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Rachitic changes were present as late as the fourteenth year, and the incidence was higher among children dying from acute disease than in those dying of chronic disease.

The authors conclude, "We doubt if slight degrees of rickets, such as we found in many of our children, interfere with health and development, but our studies as a whole afford reason to prolong administration of vitamin D to the age limit of our study, the fourteenth year, and especially indicate the necessity to suspect and to take the necessary measures to guard against rickets in sick children."

\*R H Follis, D. Jackson, M. M Eliot, and E A Park Prevalence of rickets in children between two and fourteen years of age, Am J Dis. Child 66 1-11, July 1943.

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## ANNUAL ORATION

### MEDICINE'S RESPONSIBILITY IN THE PROPAGATION OF POOR PROTOPLASM\*

ALLEN S. JOHNSON, M.D.†

SPRINGFIELD, MASSACHUSETTS

THIS unexpected and undeserved honor has made me acutely aware of my lack of fitness to wear even for this short time the mantle that has graced such distinguished predecessors. Some of them have traced with inimitable charm and grace the progress of medicine through the years. Others have granted to you imaginative glimpses of its achievements in the years to come. As neither endowment nor inclination impels me to assume the role of either historian or prophet I shall ask you to consider with me not where we have been, not where we may be going, but where we are today.

Cynics, idealists, and sentimentalists have tried to define the role of the medical practitioner. I think that most of you who are, like me, average doctors from average communities would agree that our purpose is to enable mankind to make more effective adjustments to the harassments of his environment. Whether these stresses be furnished by trauma, bacteria or psychologic tensions will determine which particular exponent of the healing art is chosen. But the ultimate goal of one and all must be the enhancement of man's capacity for environmental adaptation. Let us examine the balance sheet, then, and evaluate our contributions to man's struggle for existence today.

\* \* \*

Only with profound fear and trembling would one hint that bacterial diseases have been brought under control. Men still die of infection, and undreamed of viral and bacterial mutations may lie in wait for us around the corner. But the contemporary triumphs of modern sanitation and preventive medicine, along with chemotherapy and the more recent antibiotics, certainly warrant more optimism in this field than in some others. In the field of trauma, likewise, these advances, as well

as the contributions of the physiologist, have done much to augment the achievements of the surgeon.

Our accomplishments in the field of endocrinology are still somewhat clouded by the perplexing variety of clinical manifestations and interrelations of these systems. But the vast unexplored vistas that stretch before us should not lessen our appreciation of the concrete contributions to the control of thyroid, parathyroid and pancreatic disease for which we may pay grateful tribute to a singularly gifted group of Boston clinicians. Equally encouraging progress is being made in the field of sex endocrinology, which, unfortunately, is still sometimes obscured by commercial exploitation and premature notoriety.

Thanks to the firm foundation laid by the metabolic investigations of thirty years ago the study of nutrition has progressed from the consideration of the laboratory subject to include not merely the sick patient but also whole groups and nations suffering from dietary deficiency. The smugness of our attitude toward these accomplishments will depend upon whether we are reviving a few individuals suffering from a specific deficiency or whether we are trying to rehabilitate an entire country. We may delegate to our interns the treatment of the individual pellagrin or the alcoholic patient with polyneuritis. But the great bulk of deficiency disease today reflects the economic status of the group rather than the incompetence of their doctors and as such bids fair to be a problem for governmental administration rather than individual therapy alone.

Current propaganda on cancer might suggest to the uncritical that here is a race in which medical accomplishment is being outstripped by some malevolent force. It is true that the male death rate for cancer has shown some increase for each decade from 20 to 75 years over the past 35 years. For example, the Metropolitan Life Insurance Company reports that the cancer death rate for in-

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 23, 1948.

†Visiting physician, Springfield Hospital, Springfield.



sured groups from 45 to 75 years of age rose from 1120 per 100,000 in 1911 to 1530 per 100,000 in 1945<sup>1</sup> The cancer death rate for all ages rose from 60 per 100,000 in 1900 to 130 per 100,000 in 1940, but it must be remembered that the age group over 45 years, in which the greatest incidence of cancer occurs, increased 67 per cent<sup>2</sup> during the same 40-year period Furthermore the lay public and the medical profession have grown increasingly cancer conscious during this period, and this fact, coupled with improved diagnostic methods, probably accounts for some of the statistical increase in cancer deaths Fortunately, there is a more hopeful aspect to the problem, which suggests that our intensive efforts are bearing fruit During the period from 1911 to 1945, which showed an increase in male deaths from cancer, there was actually a slight decrease in female cancer deaths And during the past ten years even the male death rate from cancer has begun to level off<sup>1</sup> In this connection it is interesting to examine the cancer mortality trends for the last 12 years, adjusted to the age distribution of the total population and classified according to the site of the origin of the neoplasm Whereas in both sexes there is still an annual increase in deaths from cancer of the respiratory tract, there has been a steady decline in deaths due to cancer of the skin, buccal cavity, stomach and liver Cancer education and improved medical and surgical care have played a large part, but Potter<sup>3</sup> believes that the decrease in deaths from gastric cancer is greater than could be expected from these factors alone The work of the Kennaways<sup>4</sup> suggests that gastric cancer arising after the second 25 years of life may be predestined by factors to which the body was exposed during the first 25 years Potter<sup>3</sup> has pointed out that the change in the death rate from gastric cancer began about 1926, some twenty-five years after significant changes took place in the American dietary,<sup>5</sup> and suggests that there may be a causal relation This raises a new hope of rational prophylaxis, which, with improvements in diagnostic technic and the therapeutic advances implicit in the recent developments of atomic physics, may still further lower the death rate from malignant tumors

Whether or not we appear to be extending man's span of life will depend somewhat on our point of view The pediatrician will point with justifiable pride to the fact that the life expectancy of the newborn white male was 64.44 years in 1945 as compared with 48.23 years in 1900 His sister had an even better outlook by several years At 40 years in 1945 he had thirty years more ahead of him, which was only 3 years more than the 40-year-old male could expect in 1900 But the life expectancy of the 65-year-old man in 1945 was scarcely a year better than that of his father in 1900<sup>6</sup> It appears that the geriatrists can hardly join in the pediatricians' boasting Our control of the infectious

hazards of childhood and early adult life seems to have had little effect on the wearing-out process But whereas the death rate from cardiovascular renal disease has risen from 310 per 100,000 in 1900 to 495 in 1940, an increase of 62 per cent, the proportion of the population over 45 years of age has risen during the same period from 17.8 to 26.5 per cent, an increase of 67 per cent<sup>2</sup> The Metropolitan Life Insurance Company therefore concludes that "The death rate from this group of causes, corrected for the aging of the insured population, dropped virtually 30 per cent (at ages 1 to 74 years) between 1911-1915 and 1940-1944"<sup>7</sup> Although these figures suggest that the current furor about the rising death rate from degenerative vascular disease is misleading, the insignificant increase in expectation of life at 65 years of age today as compared with the figure 45 years ago indicates that immortality is not just around the corner Perhaps this is just as well The catastrophic implications of physical immortality stagger the imagination Already the social and economic dislocations produced by an ever-increasing number of old people in our population is causing concern Imagine the chaos if the aged never died off while even the puny birth rate attributed to college graduates continued<sup>1</sup> Of course even the most enthusiastic geriatrist would blanch at this prospect, but he is inclined to be a little vague when asked to what age it would be socially and individually desirable to extend life expectancy if we had it in our power to do so Perhaps our goal should be the enrichment of living rather than the mere prolongation of life This appears certainly to be more nearly within our grasp, and our contributions in this direction may atone in part for our failure to render man immortal

All this, then, and man's ability to exist at extremes of temperature and barometric pressure bear testimony to medicine's contribution to his physical capacity for environmental adaptation, What of his psychologic adjustments? Has his mental and emotional equipment kept pace with the ever-increasing complexity of his environment? Has science, which has increased the psychologic stresses to which he is subject, helped him to develop behavior patterns of comparable effectiveness? The answer to this question will depend a good deal on what sort of measuring stick we use No one really knows how many maladjusted people there are in his community, though the average practitioner may be inclined to venture a considerably higher estimate at the end of a busy day than at its beginning But even his casual estimates are dependent on the economic status of his clientele and on his own insight Rusk<sup>8</sup> has stated that there are eight million people disabled by mental disease in this country, but the usefulness of this figure depends upon one's definition of disability Selective Service rejections offer a more precise measure

of serious defects in our citizens' mental equipment. During the last eighteen months of the recent war, when the need for dwindling manpower made us progressively less critical of man's frailties, the Selective Service boards rejected 44 per cent of the 5,767,000 examinees, 26.8 per cent of these rejections were for mental disease, 2.6 per cent for mental deficiency, 4.1 per cent for neurologic disorders and 12.8 per cent for subminimal intelligence.<sup>9</sup> In other words, 46.3 per cent of all men rejected were deemed unfit on neuropsychiatric grounds to participate in the struggle for biologic survival. Not all of these were incapable of earning some sort of living or of making some degree of adjustment to their social group. Many were capable of defending themselves individually in a somewhat protective and paternalistic society. But they were deemed incompetent to participate in any such collective defense as was demanded for our survival as individuals and as a nation. In other words, they could not be relied upon to make up a winning team.

Forty-six per cent may seem like a high figure, but Selective Service boards were certainly not being unduly critical when manpower was so urgently needed. They may have been overzealous during the early part of the war, but this is not borne out by figures for medical discharges from the armed forces. During the three-year period of hostilities (1942-1945), 956,232 enlisted men were separated from the Army on certificates of discharge for disability, 379,486 (39.69 per cent) of these were for neuropsychiatric reasons.<sup>10</sup> During the same period the Navy gave medical discharges to 318,798 Navy and Marine Corps personnel, and 104,735 (32.9 per cent) of these were for neuropsychiatric reasons.<sup>11</sup> In other words, in spite of attempts at preliminary screening by Selective Service boards, which eliminated nearly half of those called up, more than a third of these were rejected later, on admittedly neuropsychiatric grounds. These figures probably err, if at all, on the side of conservatism, for all of us who sat on "survey boards" were well aware of the frankly psychiatric character of many of the visceral symptoms that earned for their hosts a nonpsychiatric discharge.

The apologist will suggest that war is abnormal and no fair test of a man's social usefulness, even though it may well test the fitness of a society to survive. What is the incidence of serious maladjustment in civilian life? It would be interesting if we could examine from the psychiatric standpoint all members of a small town as the United States Public Health Service has recently done from the standpoint of diabetes. What would be the incidence of major mental disease and of the less serious types of neuropsychiatric disorders? At present we can form only a rough estimate of the burden that institutionalized nervous and mental disease imposes on society. In the United States in 1946

the hospitals for nervous and mental diseases had 46 per cent of all the hospital beds, and the general hospitals only 43.7 per cent. During the same year the former provided 232,055,685 treatment days, or 51.3 per cent of the daily patient load, compared to 181,232,355 treatment days given by general hospitals.<sup>12</sup> This cannot be attributed to the effects of the war, since the figures for 1936 show that hospitals for nervous and mental diseases provided 192,147,438 treatment days, representing 59 per cent of the daily patient load for all hospitals. Since then general-hospital beds have increased faster than those of the institutions for nervous and mental diseases, but the proportions are still roughly the same. In Massachusetts in 1946 hospitals caring for feeble-minded, epileptic and mentally diseased patients had 50 per cent of the total hospital beds and carried 56 per cent of the daily treatment load of all hospitals in the Commonwealth at a cost of somewhat over \$14,000,000.<sup>13</sup> If we add to the 10,883,205 patient days in these Massachusetts hospitals in 1946 the man days spent in penal institutions, we may have some idea of the magnitude of this problem of maladjustment and the burden on the remaining few of us who have thus far managed to stay out of institutions.

One might conclude that the mental equipment of much of the population has not kept pace in its capacity for appropriate response with the increasing complexity of the environment. We might, for lack of a better scapegoat, blame science for this complexity. Those who have tried to understand a painting by Dali or the writings of Gertrude Stein might feel that the arts, too, must share the blame for this confusion. But these bizarre expressions can be escaped, unlike the noise of machinery, the speed of traffic, the split-second timing of assembly-line technique and the stresses, both social and economic, of a highly competitive society.

Has science attempted to atone for its responsibility by assisting the less well endowed to make more adequate adjustments? Certainly, the acknowledgment of this responsibility is reflected in the growth of psychiatric clinics, special schools for the handicapped, personnel counselors and so forth, but they reach a relatively small proportion of the needy. Much of the expenditure in the field of nervous and mental disease today is allocated to mere custodial institutional care. It is probably true that these misfits are cared for more cheaply, more effectively and with less risk to society than if allowed to run loose. It is open to question whether all these institutions are indoctrinated with the idea of rehabilitation. It is certain that the scanty budgets of many make it almost impossible. As a result many patients are released as soon as they are no longer an obvious menace to themselves or their social contacts although little has been done for long-term rehabilitation. The question may some- ra

whether this protection and perpetuation of poor protoplasm by humanitarian institutions is handicapping society as a whole both economically and genetically. Sooner or later, if present trends continue, society will have to develop methods for enabling this growing horde to effect more adequate social adjustments or else take steps to reduce their appalling fecundity. It is an interesting commentary on our social organization that two antithetical forces like war and humanitarian institutions should protect the unfit at the expense of the fit. Yet we stage a war every twenty-five years and demand that only the physically fit and psychologically well adjusted be allowed the privilege of dying for their country. The unfit are protected to perpetuate the race. The inadequate personality is sustained inside and outside institutions by a variety of federal, state and municipal agencies. Even an indisposition to work seldom results in starvation. The unfit is not wanted by the Selective Service board, and even if he leaks through its wide-meshed screen and withstands the imprecations of his superiors he is seldom assigned to dangerous or fatal duty because he is incompetent and irresponsible. He may be shorn of prestige and material goods, but his voting and procreative powers remain unimpaired and he and his multitudinous

offspring bid fair to be with us always and in ever-increasing numbers. Not all of them can be institutionalized, and not all of them need to be. But they and their problems of adjustment to society constitute a real if unrecognized task to which medicine must shortly apply itself if our contributions to man's psychologic adjustments are to keep pace with our contributions to his physical adaptations.

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## CHRONIC THYROIDITIS\*

SAMUEL F. MARSHALL, M.D.,† WILLIAM A. MEISSNER, M.D.,‡ AND DELBERT C. SMITH, M.D.§

BOSTON

CHRONIC thyroiditis, as evidenced by degeneration and fibrotic changes in the thyroid gland, is not a common disease entity but is encountered fairly frequently by the clinician and surgeon experienced in thyroid disease. The recognition of this pathologic process in the thyroid gland is important from the clinical aspect because its firmness, adherence and increase in size of the gland may cause it to be mistaken for malignant neoplasm arising in the thyroid gland.

Classification of this type of thyroid disease has always been more or less troublesome, and loosely used and poorly defined terminology has contributed in no small way to the confusion and disagreement regarding thyroiditis.

More than half a century has passed since Bernhard Riedel,<sup>1</sup> a German surgeon in Jena (1896), presented his original report on the condition of the thyroid gland that has since retained his name and has come to be known as Riedel's struma.

Sixteen years later, Hashimoto<sup>2</sup> reported what he considered to be a distinctly separate clinical and pathologic entity, struma lymphomatosa. Since these original reports, many articles have appeared in the literature concerning chronic thyroiditis, but little has been added to the knowledge of its etiology. Likewise, the clinical and pathologic picture, as known today, has changed little from the original descriptions.

Riedel<sup>1</sup> pointed out in his first report of 2 cases that the gland was of woody hardness and densely adherent to the trachea and surrounding blood vessels and nerves, all of which made it difficult to distinguish from a malignant lesion.

Hashimoto's<sup>2</sup> original report consisted of 4 cases, all in women over forty years of age, who presented essentially the clinical picture as it is known today. He was aware of the absence of inflammatory reaction and the lack of adherence to surrounding structures. He went further to point out the post-operative picture of myxedema, which disappeared after the internal administration of thyroid substance. The chief pathologic findings described were diffuse lymphocytic infiltration, atrophy of

\*Presented at the annual meeting of the New England Surgical Society Providence, Rhode Island October 3, 1947.

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the acinar epithelium, with absence of colloid, and proliferation of connective tissue

Despite the clarity with which these authors described two distinctly separate clinical entities, much confusion has occurred. This has been the result of the many variants in the microscopical picture as well as in the clinical findings. The purpose of this paper is not to give a historical review of the numerous controversies existing over the years or of the literature, but to present a summary of a pathological and clinical study of a group of cases encountered in which operation was performed at the Lahey Clinic during the period of 1928 to 1946, inclusive. As every surgeon knows, these cases may present some perplexing problems in technique at the operating table. The present study was undertaken with the hope that certain conclusions could be reached from the observation of a fairly large series of cases that would be of value in the diagnosis and further management of these patients.

During the eighteen-year period under consideration 187 cases of undoubted chronic thyroiditis were encountered in the pathological examination of the specimens from approximately 25,000 patients requiring thyroidectomy. There were many other cases in which a tentative diagnosis of thyroiditis was made on the excised tissue, but since a careful pathological review and reclassification of these specimens revealed them to be lacking in many of the characteristics thought necessary to establish this diagnosis, they were discarded in the study of this material. Also, no cases of thyroiditis occurring in hyperplastic goiter, adenomatous goiter or thyroid tumor are included, although the condition may complicate such already diseased glands. It is evident that this condition is by no means rare, since this represents an incidence of 0.75 per cent. These 187 cases, selected after careful correlation of the clinical findings with the microscopical picture, form the basis of our report.

Many other cases were found in which a clinical diagnosis of thyroiditis was made, but these patients were not submitted to operation, so that pathological examination could not confirm the accuracy of this diagnosis and, of course, they cannot be included in this study. There can be no doubt that with sufficient experience in the disease a fairly large number of cases can be recognized clinically and that, in the event of no complications, operation can safely be avoided. Because of enlargement of the thyroid gland, development of pressure symptoms, constriction of the trachea or inability definitely to exclude cancer, however, a certain number of patients must submit to operation either to decompress the trachea or to rule out malignant degeneration. Some of these patients came to surgery with enlarged thyroid glands that were mistakenly construed by the clinician to be adenomatous goiter. A correct preoperative diag-

nosis of thyroiditis in the group of 187 cases was made in only 44 patients, or 23.5 per cent, so that the preoperative error in diagnosis of patients submitted to operation is considerable. It is also well to emphasize the fact that the uncertainty regarding the type of thyroid disease present necessitates biopsy or resection of the thyroid gland, and this very fact accounts for the low percentage of correct preoperative diagnosis in this group of operated cases. In many cases the pathologist has difficulty diagnosing the condition correctly without microscopical study. Dr. Frank H. Lahey has often described the characteristics that enable thyroiditis to be recognized clinically in a large number of cases, but the necessity for repeated periodic examinations has also been constantly emphasized. Operation is demanded when even the slightest suspicion of a malignant lesion exists, and progressive enlargement or constrictive symptoms occurring in a previously clinically recognized thyroiditis may also require surgical interference at some time after the initial diagnosis has been established.

#### PATHOLOGY

Concerning the pathology of the various forms of thyroiditis it should be pointed out that there are apparently several ways in which the gland may react to injury or irritation. These basic types of reaction are seen whether the injury is the result of actual infection, trauma, vascular disturbances or altered physiology. Either the stroma or the epithelium of the thyroid gland may show considerable change in response to irritation or injury. The stromal changes consist of fibrosis and infiltration with inflammatory cells, of either mononuclear or polymorphonuclear type. The epithelial changes consist of diminution in the size or atrophy of the acini, acidophilia of the thyroid cells to become the Hürthle type and occasionally epidermidization of the epithelium. At times colloid is allowed to spill out of the follicle into the stroma, since colloid is an irritant, it causes an inflammatory response, with a foreign-body, giant-cell reaction, when it is free in the stroma.

Examples of such changes are seen in the pathologic states of hyperplasia, adenomatous goiter and tumor. In hyperplasia there is frequently an infiltration with lymphocytes and often the formation of secondary lymph follicles. A small amount of fibrosis often accompanies the lymphoid infiltration particularly in the later stages of involution. The so-called "exhaustion atrophy" of the thyroid gland is a state that presumably follows overactivity, and in this condition there is not only infiltration with lymphocytes and some fibrosis but also frequently an acidophilia of the epithelium.

In adenomatous goiter, fibrosis of the gland owing to hemorrhage or colloid spillage is frequent. Not uncommonly lymphoid infiltration and compression of the acini adjacent to the capsule of the

tumor are found in adenomas. In malignant tumors there is, of course, the inflammatory exudate frequent in cancers.

At times the thyroid gland is the site of similar basic inflammatory changes, which apparently are not associated with hyperplasia, adenomatous goiter or tumor. It is this group, called chronic thyroiditis, with which the present study is involved, cases



FIGURE 1 Infection of the Thyroid Gland in the Subacute Stage in a Forty-Six-Year-Old Man Who Complained of Pain and Swelling in the Thyroid Region of Five Weeks' Duration. Note the numerous polymorphonuclear neutrophils in the stroma and in the large acinus at the lower right. Fibrosis and foreign-body giant cells (hematoxylin and eosin,  $\times 50$ ).

that showed a definitive type of pathologic change in addition to inflammation were not included.

Excellent discussions and reviews of the pathology of chronic thyroiditis can be found in detail in the papers of Womack,<sup>3</sup> McClintock and Wright,<sup>4</sup> Joll<sup>5</sup> and others,<sup>6, 7</sup> and a lengthy description is unnecessary here. For the purposes of clinical comparison, it was found that cases of chronic thyroiditis could easily be segregated into three main groups, which were reasonably distinct both pathologically and clinically. The great majority of cases fall fairly easily into one of the three categories. The more important characteristics of each group are described below.

#### Group I

This group consisted of 41 cases showing a reaction that seemed to be due obviously to infec-

tion. It is well known that acute infections of the thyroid gland occur, but since such a gland is not removed surgically in the acute stage of an infection, no acute infections were present in this series. A group of 18 glands, however, showed changes that may be called subacute inflammation (Fig 1), there was a moderate degree of fibrosis with numerous inflammatory cells, chiefly polymorphonuclear neutrophils often centered in acini. Such acini usually showed degeneration and spillage of colloid with foreign-body, giant-cell response, although the latter cells were not numerous in this stage. In the chronic stage of the infection represented by 18 other specimens (Fig 2), the polymorphonuclear leukocytes had largely or completely disappeared, but numerous foreign-body giant cells were still present reacting to colloid. Also scattered throughout the fibrotic stroma were numerous lymphocytes and plasma cells. The fibrotic stage of the infection apparently represents the healed stage



FIGURE 2 Infection of the Thyroid Gland in the Chronic Stage in a Thirty-Seven-Year-Old Woman Who Had Soreness and Enlargement in the Neck for Four Weeks and a Tonsillectomy for Chronic Tonsillitis One Year Previously. Note the numerous foreign-body giant cells (hematoxylin and eosin,  $\times 50$ ).

(Fig 3), and in this terminal phase foreign-body giant cells were usually absent and other inflammatory cells few in number—it is this stage that usually has been designated as Riedel's struma. In none of the stages in this group was the epithelial change characteristic, and although considerable epithelium was apparently destroyed and replaced by the infection and subsequent fibrosis, that which remained usually showed little or no change

and no evident atrophy. Acidophilia was absent or slight, there was occasional epidermidization. Grossly, the glands in this group were all firm, fibrous and often gray or white. The capsules in most specimens were adherent both to the thyroid gland and presumably to the adjacent structures, since they were infiltrated microscopically with the inflammatory process. The change in the gland was sometimes focal, but often diffuse.

### Group II

The second group was composed of 78 thyroid glands, which were generally designated as Hashimoto's struma or struma lymphomatosa. This group pathologically showed a marked infiltration of the stroma with lymphoid cells and the formation of numerous secondary lymph follicles (Fig 4). The lymphoid infiltration in these glands was often little more than that seen in many cases of primary

fibrosis, in small strands and cords, the fibrosis was in broader bands only when pronounced, as in the first group. Grossly the specimens in this category averaged about 100 gm in weight for the two lobes (Fig 5). They had a rubbery consistence.

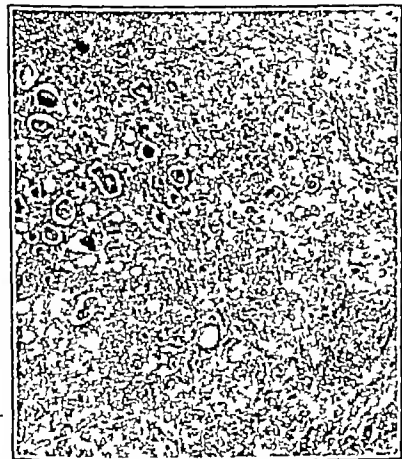


FIGURE 3 Infection of the Thyroid Gland, Largely Healed, in a Fifty-Two-Year Old Woman Who Had Swelling in the Neck with Difficulty in Breathing for Four Years and with Restricted Breathing on Raising the Arms While Combing Hair. Note the marked fibrosis. Many of the remaining acini are little changed (hematoxylin and eosin  $\times 50$ ).

hyperthyroidism, and such a marked lymphoid infiltrate is not sufficient evidence in itself to warrant placing the gland in this general group. The specimens, in addition to the lymphoid infiltration, uniformly showed atrophy and marked acidophilia of the epithelium. Occasionally there was some degeneration of colloid with foreign body giant-cell reaction, but this was inconstant. Although the stroma always showed at least a small amount of



FIGURE 4 Struma Lymphomatosa in a Forty-Six-Year Old Woman Who Had Had Cough for Three Years Increasing in Size for the Past Year, with Occasional Coughing and Choking Spells and with Difficulty in Breathing on Exertion. Note the characteristic marked lymphoid infiltration and atrophy of epithelium (hematoxylin and eosin  $\times 50$ ).

The change was diffuse and homogeneous throughout both lobes. The capsules were grossly preserved with no suggestion of adherence.

### Group III

This was a conglomerate group and undoubtedly included thyroiditis resulting from several causes. The specimens showed little that was characteristic grossly. Microscopically, they showed the basic stromal (slight fibrosis and round-cell infiltration and occasionally spilled colloid) and epithelial (absent or mild acidophilia and atrophy) changes common to all injuries of the thyroid gland, but the changes were of such a mild degree that a further classification was not possible. It seemed best to designate this group of 68 cases as simply "chronic thyroiditis, nonspecific." Two cases of thyroiditis presumably due to irradiation and 1 case of probable syphilis of the thyroid gland were not included. There were no examples of tuberculosis of the gland.

Some of the thyroid glands in this group appeared similar to the "exhaustion atrophy" state, although a history of previous hyperthyroidism was unusual. Other glands suggested that the inflammatory response was the result of a mild infection, which was not severe enough to warrant inclusion in Group I. Still other specimens must have represented an early stage of struma lymphomatosa, but with changes too mild to be pathognomonic. Vascular changes were considered a possibility as

rather indefinite mild inflammatory changes, which must be designated as nonspecific chronic thyroiditis.

### SYMPTOMS

The outstanding symptoms presented by patients with chronic thyroiditis in this series were more or less similar in all three groups of cases. The most common complaint was that of goiter or enlargement of the neck (Table 1), and was the initial complaint of 80 per cent of the patients. Local manifestations of thyroid disease were pressure symptoms, breathing difficulties, choking sensation and difficulty in swallowing in a much smaller percentage, and were present in the majority of the more advanced or more chronic cases. Neck discomfort was outstanding in the cases of infection thyroiditis (Group I), occurring in 1 in 4, and this is to be expected in view of the marked tendency to fibrosis and constriction in this type of thyroiditis. Alteration of the general physical condition, which was not a prominent feature unless myxedema was present and which occurred infrequently in the form of nervousness or fatigue, was observed more often in patients with a strong tendency to neurosis or phobia of cancer. The average duration of symptoms in all groups was approximately two years.

Diagnosis is established by the presence of an increase in size of the thyroid gland. It may be

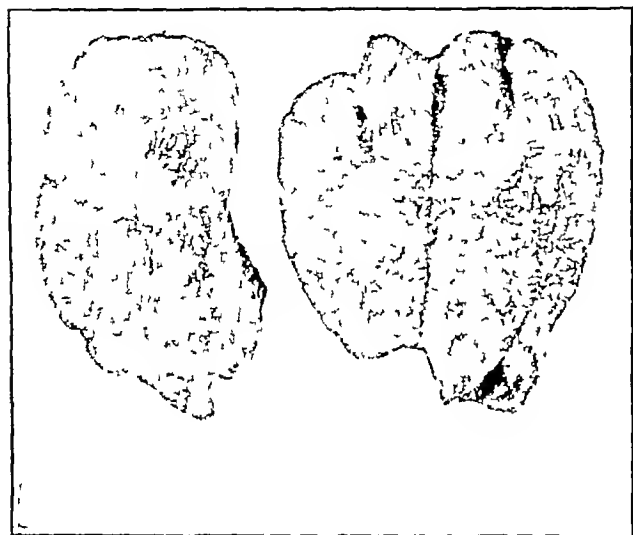


FIGURE 5 *Struma Lymphomatosa* in a Sixty-One-Year-Old Woman Who Complained of Marked Swelling in the Neck of One Year's Duration

Note the lobulation and the thin capsule

an etiologic factor in this group, but no changes could be found that could be directly attributed to vascular lesions. Still another etiologic possibility is trauma.

It is possible, then, to divide chronic thyroiditis into three groups pathologically. Group I includes cases of thyroiditis in the true sense—that is, inflammation of the thyroid gland caused by actual infection. The terminal or healed stage of this type of thyroiditis has been known as Riedel's struma, but it seems more logical to include all stages of infection of the thyroid gland under one grouping no matter whether the infection is acute, subacute, chronic or healed. Group II, composed of specimens that have previously been designated as struma lymphomatosa, appears to be distinct and separate from thyroiditis caused by infection. The pathological changes are characteristic enough in most cases to warrant a separation of these specimens from the other types of thyroiditis, although the etiology is unknown. In addition to these two groups, which present more or less specific pictures pathologically, there is the third group of

TABLE 1 *Presenting Symptoms in Cases of Chronic Thyroiditis*

SYMPTOM	GROUP I NO. OF CASES	GROUP II NO. OF CASES	GROUP III NO. OF CASES
Goiter or enlargement in neck	30	66	53
Difficulty in breathing	4	12	4
Pressure sensation	3	10	11
Nervousness	8	8	6
Fatigue	9	7	4
Cough	2	6	4
Hoarseness or change in voice	4	6	3
Discomfort in neck	10	4	7
Choking sensation	0	4	7
Difficulty in swallowing	2	3	

fairly large (two to four times the size of the normal gland) and firm, and this feature is characteristic of all three groups. The enlargement is bilateral in the majority of cases (occasionally it is unilateral in Riedel's struma) and is symmetrical. The anatomic outline of the lobes is maintained, as is the sharp apex of the upper pole where the superior thyroid vessels enter. The firmness of the gland in Riedel's thyroiditis may be very marked, it is woody or stony hard, with a tendency to adherence to the trachea and surrounding structures, and gives to the examiner a sensation of immobility. The induration of struma lymphomatosa is more elastic and resilient but still quite firm, it is not accompanied by the adherence to surrounding structures noted in the first group. The differentiation from

cancer in the majority of cases of all groups can be made readily, but it is well to point out that cancer cannot definitely be ruled out in a small percentage of cases, and these patients must submit to surgical interference consisting of either biopsy or partial resection of the gland. Thyroiditis usually arises in a presumably normal gland, which has not previously been the seat of a goiter, and no

marked lymphoid infiltration with little or no secretive epithelium of Hashimoto's struma represents the healed or end stage of the process in these two groups. There is no evidence that in the chronic stage of thyroiditis acute inflammatory changes will develop. Fever does not accompany the process of chronic thyroiditis, and signs of inflammation such as redness and marked tenderness

TABLE 2. Data in Cases of Thyroiditis Due to Infection (Group I)

STAGE OF THYROIDITIS	NO. OF CASES	AGE OF PATIENTS			SEX OF PATIENTS		AVERAGE DURATION OF SYMPTOMS	CORRECT PER OPERATIVE DIAGNOSIS	CASES OF PRE-OPERATIVE HYPOTHYROIDISM	CASES OF POST-OPERATIVE HYPOTHYROIDISM	CASES OF POSTOPERATIVE COMPLICATIONS		
		YOUNGEST	OLDEST	AVERAGE	MALE	FEMALE					TRACHEOTOMY	TETANY	RECURRENT LARYNGEAL PARALYSIS
Subacute	18	37	37	37	4	14	ma.	%	%	%	-	-	1
Chronic	16	36	53	44	4	14	17	55	11	11	-	-	-
Healed	7	29	70	46	6	10	6.0	63	6	37	-	1	-
		26	63	49	1	6	23.0	43	29	57	-	-	-
Totals	41				11	30					-	1	1
Averages		26	70	46			9.6	56	7	27			

history of nodular goiter can be obtained. Carcinoma arises commonly on the basis of an adenoma, and consequently the gland is usually nodular from the beginning. As the malignant growth involves and breaks through the capsule, the gland loses its anatomic outline and symmetry, and ordinarily the neoplasm involves one lobe or the isthmus and the fixation is local over the tumor and does not possess the symmetrical fixation of Riedel's thyroiditis. If the clinical diagnosis of thyroiditis can be reasonably assured or if a biopsy specimen

in the neck are not described nor have we been able to obtain the history of such local inflammation in any of the cases in this group. Spontaneous regression of the inflammatory process probably also does not occur.

#### SEX DISTRIBUTION

It is well known that the thyroiditis described by Hashimoto is rarely seen in men, and in the group of 78 cases, only 1 occurred in a male patient (1 male to 77 females), whereas infectious thyroiditis

TABLE 3. Data in Cases of Struma Lymphomatosa (Group II)

DEGREE OF THYROIDITIS	NO. OF CASES	AGE OF PATIENTS			SEX OF PATIENTS		AVERAGE DURATION OF SYMPTOMS	CORRECT PER OPERATIVE DIAGNOSIS	CASES OF PRE-OPERATIVE HYPOTHYROIDISM	CASES OF POST-OPERATIVE HYPOTHYROIDISM	CASES OF POSTOPERATIVE COMPLICATIONS		
		YOUNGEST	OLDEST	AVERAGE	MALE	FEMALE					TRACHEOTOMY	TETANY	RECURRENT LARYNGEAL PARALYSIS
Mild	12	37	37	37	—	12	ma.	%	%	%	—	1	—
Moderate	36	29	58	45	—	36	23	14	11	50	1	1	—
Marked	30	31	71	52	1	29	74	27	7	77	1	1	3
		33	69	51	1	77	28			93	2	2	5
Totals	78				1	77							
Averages		29	71	50			26	17	8	79			

is obtained to establish the absence of neoplasm, there is no evidence that the malignant degeneration is likely to develop in a gland involved with thyroiditis. The various stages of degenerative and fibrotic changes noted on pathological study in Groups I and II may well indicate that the disease is progressive in character and that the advanced sclerotic, woody gland of Riedel and the

(Group I) may occur in either the male or the female (Tables 2 and 3). About half the cases in the literature are said to have occurred in men, in our series there were 11 males to 30 female patients. In the cases of nonspecific thyroiditis (Group III) there were 3 males and 65 female patients (Table 4). We have no data to indicate whether the sex distribution in these cases was significant, but since thyroid



disease is more common in women, the tendency of greater incidence in female patients may not be especially helpful in diagnosis of thyroiditis and may not be especially significant. In view of the infrequency of Hashimoto's thyroiditis in men, however, it is extremely unlikely that a preoperative

but these patients should be observed at stated intervals for evidence of compression of the trachea and to exclude the possibility of overlooking malignant tumors. If treatment is indicated in any case, we believe that operation offers the best method. It should consist of either partial resection of the

TABLE 4 Data in Cases of Nonspecific Thyroiditis (Group III) \*

No. of Cases	AGE OF PATIENTS			SEX OF PATIENTS		AVERAGE DURATION OF SYMPTOMS	CORRECT PREOPERATIVE DIAGNOSIS	CASES OF PREOPERATIVE HYPOTHYROIDISM	CASES OF POSTOPERATIVE HYPOTHYROIDISM
	YOUNGEST	OLDEST	AVERAGE	MALE	FEMALE				
68	37 12	57 75	37 43	3	65	22 mo	12 %	6 %	50 %

\*No postoperative complications occurred in this group of cases

diagnosis of struma lymphomatosa could be made correctly in men

AGE

The average ages for the three groups of cases were essentially similar and were not especially significant. Thyroiditis of the infectious type or of

gland or excision of the isthmus to relieve constriction of the trachea. We have not treated any of these patients with irradiation although there are some reports of good results in the literature. We believe that additional fibrosis produced by the reaction of irradiation may well increase the constriction on the trachea and also further destroy remaining thyroid-secreting epithelium. The principal indications for surgery are definite pathologic evidence that the process is not malignant and relief of pressure symptoms or release of tracheal constriction. In most cases of Riedel's thyroiditis the diagnosis can be established at the operating

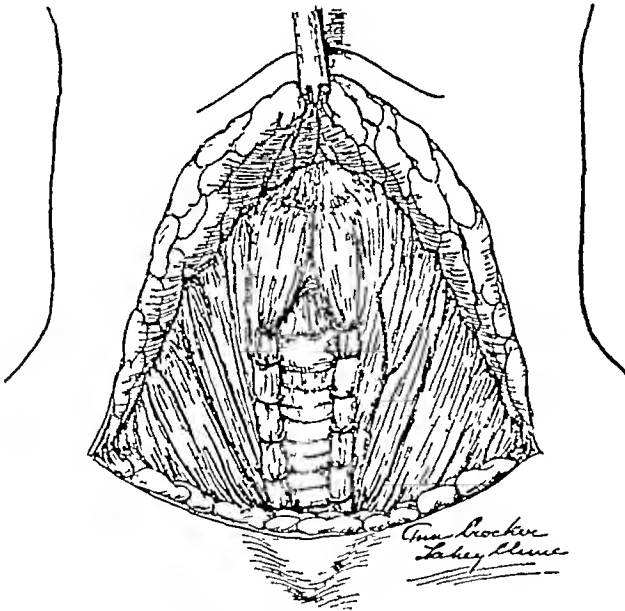


FIGURE 6 Stage in Operation for Chronic Thyroiditis. The isthmus and medial portions of both lobes have been removed to clear the anterior part of the trachea of all thyroid tissue. The sternohyoid muscles have been sutured to the trachea to prevent adherence of the lateral lobes and recurrence of compression.



FIGURE 7 Narrowing of the Trachea Caused by Compression from Chronic Thyroiditis (Reprinted from Lahey<sup>8</sup> by Permission of the Publishers)

the Hashimoto type is rarely seen before the age of thirty-five, but may occur at any age thereafter (Table 2)

TREATMENT

We have already called attention to the fact that diagnosis can be made in a large number of cases and that treatment in many cases is unnecessary,

table by the appearance of the thyroid gland upon exposure and by its adherence to surrounding structures, and biopsy can immediately confirm this. Radical resection is unnecessary, and may be difficult because of the stony hardness of the gland and the difficulty in dissection and exposure of the normal structures such as the recurrent laryngeal

nerves and parathyroid glands. If radical removal is persisted in when marked induration and adherence are present, serious complications may result from injury to the parathyroid glands and to the recurrent laryngeal nerves. Furthermore, release of pressure on the trachea can be obtained by simple removal of the thyroid isthmus, as proposed by Lahey,<sup>8</sup> which separates the lobes and releases the vise-like pressure on the trachea. Suture of the prethyroid muscles to the tracheal fascia prevents the lobes from becoming adherent to each other with return of pressure on the trachea (Fig. 6). Inasmuch as active thyroid-secreting epithelium is still present in the sclerosed gland in Riedel's thyroiditis, extensive partial removal is undesirable, since this procedure decreases thyroxin secretion still more and increases the number of cases in which myxedema develops.

Bilateral partial thyroidectomy is advisable in Hashimoto's struma and should be radical enough to relieve the compression (Fig. 7) noted in these cases as well as to improve the cosmetic effect by removal of an enlarged gland. Large remnants of either lobe should be allowed to remain to avoid injury to the recurrent laryngeal nerves or parathyroid glands, although the lack of adherence of the gland precludes much risk. It is evident that a radical resection in these cases will result in earlier signs of myxedema, but many of these patients exhibit hypothyroidism before operation, practically all patients (7 per cent preoperatively and 27 per cent postoperatively in Group I, 8 per cent preoperatively and 79 per cent postoperatively in Group II and 6 per cent preoperatively and 50 per cent postoperatively in Group III) develop myxedema later regardless of how much thyroid tissue is removed. It matters only that sufficient tissue be removed to relieve pressure symptoms and constriction of the trachea, we believe that this can be done best by a liberal partial thyroidectomy.

#### TYPE OF OPERATION

From this discussion, excision of the thyroid isthmus is considered sufficient in most cases of infection thyroiditis, and a partial bilateral thyroidectomy is desirable in struma lymphomatosa. The best procedure in patients in Group III is excision of the isthmus, but this may have to be modified if sufficient relief of pressure cannot be obtained by such a conservative procedure. In these cases, as in Group I, every effort should be made to conserve thyroid tissue to avoid myxedema. The frequency of myxedema in the various groups after the various operative methods may well serve as a guide in planning treatment in these cases.

Thyroid deficiency is present or develops after operation in many cases. It is much less common

in the infectious type (27 per cent), but in the more advanced stage of this group (Riedel) it was noted in 57 per cent. As stated above, patients with Hashimoto's struma developed signs of thyroid deficiency in 79 per cent of the whole group, but this incidence was increased only 8 per cent if partial thyroidectomy was done. In the nonspecific group, thyroid deficiency was noted in 50 per cent of cases, but a decreased tendency (33 per cent) was noted with resection of the isthmus only. In some instances too few cases were observed to draw final and definite conclusions, but our studies seem to point to the value of conserving thyroid tissue whenever possible, except possibly in the Hashimoto type.

Postoperative complications consisted of tetany and recurrent-laryngeal-nerve paralysis (Tables 2, 3 and 4), 2 patients required temporary tracheotomy after operation for Hashimoto's struma, but this was necessary because of edema arising after operation in myxedematous patients, which is not an uncommon complication and did not follow nerve injury. In view of the possible tendency for patients with myxedema to develop postoperative edema it is wise to correct any thyroid deficiency by oral administration of desiccated thyroid before operation and thus to avoid respiratory difficulty after operation. We believe that with recognition of the necessity for exposure of the recurrent nerves in all partial resections of the thyroid gland for any cause, the complication of recurrent-laryngeal-nerve paralysis can be avoided or at least seldom encountered.

#### SUMMARY

A report of 187 cases of chronic thyroiditis is presented, and an attempt is made to analyze the clinical and pathological characteristics.

Chronic thyroiditis occurred not infrequently in our experiences with approximately 25,000 operations for thyroid disease, an incidence of 0.75 per cent.

An attempt is made to classify these cases into three groups on the basis of pathological changes noted in the excised gland and to correlate these findings with the clinical course of the patients.

Clinical diagnosis of chronic thyroiditis is possible, and it is clinically possible to distinguish thyroiditis from thyroid cancer in a large number of cases.

Treatment is unnecessary in many cases but when necessary to establish diagnosis or to relieve pressure on the trachea, surgical removal of the isthmus or partial thyroidectomy offers the best method.

Myxedema develops with the course of the disease, and operation should be planned to minimize this tendency as much as possible.

Operative complications can be avoided or decreased with a better selection of the type of opera-

tion in each case and with improvement in technic of thyroid resection

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## TUMORS OF SALIVARY-GLAND ORIGIN\*

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THIS report summarizes the experience with tumors of salivary-gland origin observed at the Massachusetts General Hospital from 1930 to 1941, inclusive, and at the Pondville State Cancer Hospital from 1927 to 1941, inclusive. Table 1 presents the distribution of the cases.

The relative frequency of carcinoma and mixed tumors of the parotid and submaxillary salivary

marily with the mixed tumors and carcinomas of the parotid and submaxillary salivary glands. Identical tumors may occur in abnormal locations about the mouth and elsewhere, principally in the cheeks, palate or lips. Their management is the same as that of the corresponding tumors of the salivary glands.

### DIAGNOSIS

The usual patient presents a symptomless tumor in the submaxillary or parotid region, discovered accidentally or because some fullness or swelling is noted. The differentiation between mixed tumor and carcinoma on the basis of history and physical findings alone is difficult and often impossible. Although the relation of mixed tumor to carcinoma is obscure, the diagnosis of carcinoma arising from mixed tumor was made on pathological study in 10 cases in the present series (16 per cent of the cases of carcinoma). In certain other cases of long duration the pre-existence of a benign tumor may be assumed. Analysis of the preoperative duration disclosed that more than half the mixed tumors were known to be present for over three years, in contrast to the carcinoma cases, in which nearly half the patients gave a history of known duration of a year or less. The mixed tumors are generally characterized as sharply defined, firm rather than hard, and movable. In contrast, the carcinomas are often less sharply defined, are usually described as hard rather than firm and are already fixed in the great majority of cases when the patient is first seen. Whereas both tumors may occur at any age, from the second to the ninth decade, the greatest concentration of mixed tumors takes place in the third and fourth decades, and the carcinomas occur principally in the sixth and seventh. Primary facial-nerve palsy was observed in 15 cases of carcinoma of the parotid gland (25 per cent), but it did not occur in the cases of mixed tumor, although in 1 case there was some twitching of the lip suggesting nerve irritation. Cervical-lymph-node enlargement was noted

TABLE 1 Tumors of Salivary-Gland Origin

TYPE OF TUMOR	PAROTID GLAND NO OF CASES	SUBMAXILLARY GLAND NO OF CASES	ABNORMAL LOCATIONS NO OF CASES
Mixed	115	16	12
Carcinoma	61	12	2
Miscellaneous	17	6	

glands is unusually high in this series of cases as shown in Table 1. This is due to the fact that more carcinomas than mixed tumors of the parotid and submaxillary salivary glands were observed at the Pondville State Cancer Hospital during the period studied. A truer incidence of the relative frequency of these tumors is shown in the Massachusetts General Hospital cases, in which there were 91 mixed tumors and 25 carcinomas of the parotid gland and 14 mixed tumors and 8 carcinomas of the submaxillary salivary gland.

The miscellaneous group comprises cysts, adenomas, sarcoma, Mikulicz's disease and various other conditions. These tumors cause confusion in diagnosis. They are sufficiently rare so that decision regarding treatment must be made on the merits of the individual case. Our present concern is pri-

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in association with 4 cases of mixed tumor of the parotid gland. Established cervical-lymph-node metastases were present in 29 cases (47 per cent) of the parotid carcinomas. Finally, the possibility of remote metastasis should be considered in cases of carcinoma. Pulmonary metastases were discovered in 4 cases of parotid carcinoma primarily, and remote disease in the lungs, skeleton, liver and other areas was observed in 12 more during the later course of the disease. These clinical con-

and an additional patient suffered facial-nerve injury. Among 15 primary and 10 recurrent cases treated by the Adson-Ott operation described above there were no recurrences or facial palsies in the primary cases, whereas there were 3 recurrences and 1 facial palsy in the recurrent cases.

The relatively large number of patients who first present themselves at the clinics with recurrence following operation elsewhere suggests that enucleation of the tumors is rather widely followed, and

TABLE 2 Clinical Data in Cases of Mixed Tumors and Carcinoma

TYPE OF TUMOR	MEDIAN AGE OF PATIENTS	MEDIAN DURATION OF TUMOR	TUMOR OF HARD CONSISTENCE	MOVABLE TUMOR	ENLARGEMENT OF CERVICAL LYMPH-NODES	PRIMARY FACIAL NERVE PALSY	REMOTE METASTASES
	%	%	%	%	%	%	%
Mixed	30-40	More than 3	30	30	3	25	25
Carcinoma	50-60	Less than 3	70	15	47	75	75

trasts between mixed tumors and carcinomas are summarized in Table 2.

It is evident from these data that in many cases the diagnosis on clinical evidence is ambiguous and that exploration must be resorted to. At the time of operation the discovery of lack of definition of the limits of the tumor, the persistence of fixation as the operation progresses and the apparent implication of the branches of the facial nerve in the tumor itself all argue for the probable diagnosis of cancer. In cases of doubt, it is necessary to resort to immediate pathological examination.

### TREATMENT

#### Mixed Tumors

In recent years there has been increasing recognition that simple enucleation of mixed tumors invites the possibility of recurrence and that simple enucleation of a tumor that proves to be carcinoma destroys the best chance of effecting a cure. The present practice is essentially that described by Adson and Ott,<sup>1</sup> in which the facial nerve is identified and exposed, and the part of the gland lying superficial to the nerve, including the tumor, is completely removed. In the cases in which the mixed tumor originates in the part of the gland lying on the deep medial aspect of the nerve, the nerve and its branches may be lifted to permit removal of the tumor-bearing area.

There were 94 primary cases of mixed tumor of the parotid gland and 21 cases with recurrent tumors after primary treatment elsewhere. Eighty-five patients with primary cases were treated by surgery, of whom 8 developed recurrences and 6 had some facial-nerve injury. Of 19 patients with recurrent tumors submitted to operation, 3 had already suffered injury to the facial nerve. Four secondary cases developed later recurrence,

that it is associated with considerable risk of recurrence and facial-nerve injury. Our own experience with simple excision or enucleation (61 cases with 5 recurrences and 3 cases of facial palsy) confirms the unsoundness of this method of management. Although some patients were treated with incomplete excision supplemented with radiation, we had no significant success with this method. However, our experience is too limited to permit evaluation of the various proposed technics of radiation as supplementary or definitive therapy for mixed tumors.

Several years ago McFarland<sup>2</sup> suggested that mixed tumors may become increasingly benign with time and growth, and that recurrence is less likely to follow operation on large tumors of long duration than operation on small tumors. Analysis of the present group in respect to size of the tumor in relation to the incidence of recurrence does not support McFarland's contention. In fact, the highest incidence of local recurrence was associated with the largest primary tumors.

There were 8 recurrences among the primary cases subjected to operation (10 per cent). All these followed operative technics that have since been discarded. All patients were submitted to a second operation, which was successful in all but 1 case, in which a third operation was necessary to effect a cure. Among the patients with secondary cases subjected to operation, there were 4 (20 per cent) in whom a recurrence took place after operation, requiring a third operation for control.

It seems unnecessary to labor the point that local recurrence is due to improper surgical technic. There was a definite notation that the tumor was encapsulated in 83 cases, and in 23 of these the tumor capsule was broken or cut into. Follow-up observation on 16 of these patients disclosed recurrence in 4 (25 per cent). There is considerable likelihood that

the incidence of recurrence is greater than these figures indicate, because a long time may elapse before the recurrence is manifested. In nearly half our cases, the recurrence took place after five years.

The mixed tumors of the submaxillary salivary gland are treated in the same way as those of the parotid gland — namely, by radical removal of the gland. Recurrence took place in only 1 case in our series, in which only a small part of the gland had been removed along with the tumor.

### Carcinomas

The treatment of carcinoma of the parotid gland depends upon the stage of the disease. In the earliest stage, the tumor is first recognized as carcinoma by the pathologist. Provided that a wide excision of the Adson-Ott type has been employed, there does not appear to be any indication for further operation at the moment. Many such cases are given a course of postoperative x-ray therapy, but review of the material does not suggest that recurrence is avoided or delayed as a result. Careful follow-up observation over a long period will detect cases that develop cervical-lymph-node metastases requiring neck dissection or that present operable local recurrence in the parotid region.

The second stage includes cases in which the diagnosis of carcinoma is made preoperatively or during the course of the operation. These cases call for radical measures at once, with sacrifice of the nerve if it is possibly implicated and with radical neck dissection. Finally, a large number of cases are inoperable when the patients are first seen, owing to wide local fixation, inoperable metastases or remote dissemination. These patients are treated with various operations or combinations of surgery and radiation, depending upon the problem presented by the individual case. The carcinomas are not particularly sensitive to radiation therapy.

The secondary cases in this series fall into two groups, those with recurrence following operation elsewhere, and a smaller group of patients who are sent for prophylactic postoperative radiation. Those with established recurrences are treated essentially like the primary cases of corresponding stage.

Among the 61 cases of carcinoma of the parotid gland, 40 were primary cases, and 21 had received treatment elsewhere. Radical removal of the parotid tumor with or without supplementary radiation, was employed in 33 cases, in which 5 patients were cured, 7 were untraced and the remainder were failures. Radical neck dissection was added to removal of the primary tumor in 7 addi-

tional cases, but there were no cures in this group. Seventeen primary cases were treated with radiation alone, with no cures. It is evident that the results of treatment are unsatisfactory and that the principal difficulty is due to the advanced stage of the disease when the patients are first seen. Analysis of the causes of failure indicates that recurrence in the operative field was the principal one, taking place in 19 cases.

There were 12 patients with carcinoma of the submaxillary salivary gland. Ten of these were subjected to surgical treatment, with or without supplementary radiation. There were no cures in this group. Here again there was failure to control the primary disease, rather than metastases. When it is realized that a large percentage of submaxillary-gland tumors are carcinomatous (Table 1), the desirability of more radical local interventions is obvious.

There were 2 carcinomas of salivary-gland origin in abnormal locations, 1 involving the palate and the other the antrum. The former case was treated by electrosurgical excision and electrocoagulation, and the other by multiple operations followed by radium and x-ray radiation. Both patients died because of failure to control the disease locally.

### SUMMARY

The experience of the Massachusetts General and Pondville hospitals with tumors of salivary-gland origin is reviewed.

The differential diagnosis of mixed tumors and carcinomas is difficult, but certain characteristics permit a presumptive diagnosis.

The treatment of mixed tumors is satisfactory provided that a wide resection of the gland is carried out. Visualization of the facial nerve is the best safeguard against injury. Enucleation of the tumor invites recurrence.

The treatment of carcinoma is unsatisfactory. Failure to establish the diagnosis in early cases results in the employment of subradical procedures and invites recurrence. A large percentage of the patients present advanced and incurable disease when they are first seen. Early wide resection of the gland offers the best chance for cure. In our experience radiation treatment is not effective.

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## CLINICAL NOTE

## THE USE OF PARA-AMINO BENZOIC ACID IN A CASE OF ROCKY MOUNTAIN SPOTTED FEVER

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PARA-AMINO BENZOIC acid was first reported in the treatment of louse-borne rickettsial diseases in 1942 by Snyder and his associates.<sup>1</sup> After experimental work on the Rickettsia of Rocky Mountain spotted fever by Hamilton, Plotz and Smadel<sup>2</sup> among others, its subsequent use in the treatment of human beings was reported by Rose et al.<sup>3</sup> and other investigators. The patient in the following case was treated according to a schedule reported by Greeley.<sup>4</sup>

## CASE REPORT

A 4½-year-old girl was admitted to the hospital on June 4, 1947, with a history of fever and rash over the upper and lower extremities of 2 days duration. One week prior to entry wood ticks had been removed by the mother from the child's head. Two days before admission a lump was noted on the back of the child's head. She complained of nausea and abdominal discomfort and vomited on two occasions on the day prior to admission and the temperature was 104 F. The child also complained of a headache and chilly sensations. She appeared to be drowsy, restless and irritable when seen by Dr. Carroll Keene of Chatham, Massachusetts, who advised hospital admission because of a rash suggestive of spotted fever.

The past history was irrelevant; there had been no recent exposure to childhood diseases.

The family history was noncontributory.

Physical examination revealed a well developed and well nourished child, complaining of headache and chills who was somewhat irritable and delirious. The head was normal except for nontender cervical lymph nodes in the posterior triangle on the right side. There was no evidence of infection in the scalp or localized areas of hematoma. The eyes and ears were normal. The nose and throat were not remarkable except for a slight, nonpurulent, nasal discharge. The lungs were normal to auscultation and percussion. The heart was normal in size, shape and rhythm. Examination of the abdomen was negative. There were no masses or areas of tenderness. The liver and spleen were not palpable. The extremities were normal. Neurologic examination was essentially negative except for some general hyperactivity. The skin showed a finely macular discrete rash scattered over the upper and lower extremities. It was located mainly below the elbows and knees becoming more pronounced toward the periphery and was present on the palms of the hands and the soles of the feet. The macules blanch on pressure and occasional petechiae were also noted. Scattered macules were observed on the chest and neck, and a few on the back and abdomen. None were seen on the face.

The temperature was 102.8 F; the pulse 100 and the respirations 22. The blood pressure was 90/40.

Examination of the blood revealed a red-cell count of 4,500,000, with a hemoglobin of 14.5 gm per 100 cc., and a white-cell count of 9000, with 68 per cent neutrophils and 32 per cent lymphocytes. Urinalysis showed a specific gravity of 1.032 and negative tests for albumin and sugar with occasional white cells noted in the sediment. The nonprotein nitrogen was 32 mg., and the blood sugar 140 mg. per 100 cc. The sedimentation rate was 20 mm. in 1 hour (Westergren method). Blood was drawn for agglutination tests for typhoid fever, undulant fever and Weil-Felix reactions. The results are reported below.

The patient was treated symptomatically with fluids and aspirin on admission. Approximately 17 hours after entry, the child was given 5 gm of para aminobenzoic acid in 25 cc. of a 5 per cent sodium bicarbonate solution. 60 cc of pineapple juice was used to disguise the acid taste of the solution. This, however, was vomited soon after ingestion. The same dosage and preparation were repeated in 2 hours, and this was also vomited. Approximately 21 hours after admission 2 gm of para aminobenzoic acid in 10 cc of 5 per cent sodium bicarbonate solution was given in 60 cc of grape juice. This was retained and continued to be retained throughout the administration of this medication at 2 hour intervals and at the same dosage for the following 6 days. Additional treatment consisted of a high protein, high-calorie diet fluids as tolerated and a preparation high in vitamin content three times a day with vitamin K injections every other day. Daily white-cell count and differential counts were done as well as daily urinalysis. Approximately 24 hours after the first successful administration of the para aminobenzoic acid the temperature had fallen to 99°F. The pulse which had varied between 120 and 160 fell to 100. Within 48 hours after the administration of para aminobenzoic acid the temperature was normal and remained so throughout the patient's stay in the hospital. The blood pressure showed no appreciable change throughout the hospital stay. The white-cell count was 9500 on the 2nd hospital day, 12,300 on the 3rd day and 10,000 on the 4th day, varying between 6700 and 11,000 on the 5th, 6th and 7th days. The neutrophil count remained between 55 and 69 per cent, with 2 to 4 per cent eosinophils on the 5th, 6th and 7th days. Daily urine tests remained negative except for an olive reaction to Benedict's solution on one occasion.

The rash responded in much the same way as when serum is successfully administered. Several areas that were petechial gradually regressed, leaving small brown spots on the skin. The macules gradually faded out and were completely gone within 5 days of entry. Response to the drug was prompt and gratifying. Blood agglutination tests taken 10 days after admission were reported as follows: Agglutination for *Proteus vulgaris* (strain X19) is positive in a dilution of 1:640 and agglutination for Rocky Mountain spotted fever is positive in a dilution of 1:16; the test for endemic typhus is negative.<sup>5</sup> Bacteriologic examination of the blood on August 19 showed that the complement fixation test for Rocky Mountain spotted fever was positive in a dilution of 1:64. The test for endemic typhus was negative.

## DISCUSSION

Although blood concentrations of para-aminobenzoic acid were not determined, the patient's response to this medication is considered to have been prompt and gratifying. This case responded in the same way as those in which antiserum is successfully used.<sup>6</sup> In our experience there have been no rapid recoveries of the disease when specific measures were not employed early.<sup>8</sup>

## SUMMARY

A case of Rocky Mountain spotted fever treated successfully with para-aminobenzoic acid is presented. No toxic effects to the drug were noted.

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## MEDICAL PROGRESS

### ALLERGY

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THE year 1947 was marked by an ever-increasing number of papers on allergy in the medical literature. These appeared not only in journals devoted to this specialty itself but also in a wide range of other medical and scientific periodicals. This broadening of the scope of allergy has not been confined to the clinical problems of the allergist, the internist, the dermatologist or the pediatrician. It has spread into the realms of pathology, biochemistry, pharmacology, immunology and immunochemistry. Investigators in these basic sciences of medicine have done much to increase the understanding of allergic reactions and to suggest the possible importance of this type of mechanism in diseases other than such commonly recognized allergic disorders as asthma and hay fever. This gradual infiltration into allied fields has helped to extend the horizons of allergy both from a practical and from a potential standpoint. It has also made it necessary for recent reviewers to confine themselves to consideration of but a few aspects of allergy at a time.

The present paper is limited to the following topics of general interest that have shown signs of progress in the field of allergy during the past year: a review of the reviews, modern immunologic and pathological concepts of allergy, histamine and antihistaminic drugs, and emotional factors.

#### REVIEWS

Recent general reviews have covered many branches of the literature. Kaplan and Ehrlich<sup>1</sup> have dealt with various aspects of hay fever. The subject of respiration has been covered by Brown,<sup>2</sup> with emphasis on several phases of this complicated mechanism, which is important to allergy.

Boyd<sup>3</sup> has reviewed recent developments in the field of immunity from the standpoint of a chemist but with special reference to the interests of the allergist, discussing the interaction of antibodies with antigens or haptens. Kabat<sup>4</sup> points out the immunochemical difficulties involved in the study of the quantitative aspects of this type of human allergic reaction. Cooke,<sup>5</sup> in discussing the immunology of allergy, provides an immunologic classification dividing such reactions into two types: the immediate or wheal-forming type, which may be of either the induced or the spontaneous variety,

and the delayed immunologic reaction, which produces an inflammatory response of the tuberculin, the dermatitic or the vascular type. Of general interest is his comment that an antigen-antibody mechanism has not been demonstrated in most of the diseases of the delayed or inflammatory type of reaction. Such a mechanism, however, is usually operative in immediate or wheal-forming disorders, such as serum disease, seasonal hay fever and extrinsic asthma.

Drug allergy has been well reviewed by Dragstedt<sup>6</sup> and by Sherman.<sup>7</sup> The latter emphasizes the point that in cases of allergy due to non-protein drugs, circulating antibodies are demonstrable only in rare cases.<sup>8</sup> Skin tests, with the exception of patch tests in contact dermatitis, are therefore of no value. In sensitization due to protein drugs or gums, however, circulating antibodies can usually be demonstrated. In such cases, skin tests by the scratch or intradermal methods may be helpful. A further point is not always appreciated. Drug fever, leukocytosis, arthralgia, lymphadenopathy and many types of skin reactions, as well as the usual allergic symptoms, are often due to drug sensitivity. The *modus operandi* of drug allergy is still under debate but is worth brief consideration. Studies by Landsteiner<sup>9</sup> and others have demonstrated that simple chemical compounds can combine with proteins and act as haptens, thereby determining the specificity of antibody reactions. This theory has helped to correlate crystalloid drug sensitivity with the more familiar protein sensitization. Chase,<sup>10</sup> however, has recently been able to sensitize guinea pigs with repeated intradermal doses of simple chemical compounds dissolved in olive or corn oil. Transfer of serum from such prepared animals to skin sites on normal guinea pigs was successful in sensitizing the latter. When such sites were tested with the original chemical, immediate wheal-forming positive reactions were obtained, often with pseudopods. Chase<sup>11</sup> also succeeded in preventing this sensitization by feeding the same chemical to guinea pigs prior to repeating the experiment described above. These observations are important in that they suggest that drug allergy may operate along the paths of the better known antigen-antibody mechanism. Further observations from the immunologic and biochemical standpoint were made and dis-

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cussed by Frazier and Small<sup>12</sup> in their consideration of allergic dermatitis

Excellent progress reports have appeared within the past year in pediatric allergy by Glaser,<sup>13</sup> miscellaneous allergy by Halpin<sup>14</sup> and dermatologic allergy by Baer and Leider.<sup>15</sup> Stevenson and Alvord,<sup>16</sup> in an analysis of allergy of the nervous system, point out that headache, somnolence and convulsions, as well as signs of focal or general disease of the central or peripheral nervous system, may be produced by hypersensitivity. Rackemann,<sup>17</sup> in a scholarly review of the 1946-1947 literature of allergy has discussed many basic and controversial concepts and has summarized several lines of progress. Unger and Gordon<sup>18</sup> have presented a critical review of the domestic and foreign literature on asthma for the same period.

#### PATHOLOGY

The recognition of characteristic histologic changes in various types of allergic disease is recent and one of the more interesting if not the most clinically valuable advance in allergy. According to Bohrod's<sup>19</sup> classification, the results of tissue injury may be anaphylactoid, necrotizing or granulomatous, depending upon various factors, which include the strength of the inflammatory stimulus, the responsiveness of the host and the velocity and the duration of the reaction. The histologic picture varies with the type of lesion. The simplest form of the immediate wheal-like reaction presents a picture characterized primarily by exudative changes such as edema and swelling of collagen fibrils. The diseases that bring this about comprise the common allergic syndromes seen in practice. The reactions are usually mild in intensity and brief in duration and leave the tissues without permanent damage. The granulomatous lesions, on the other hand, are the result of inflammation and cause more permanent damage. Their essential structure consists of a central area of necrosis surrounded by proliferative reticuloendothelial cells, which often assume a radial, palisaded arrangement. Necrotizing lesions likewise destroy tissue. They are characterized by diffuse necrosis involving parenchymal cells, interstitial tissue and vascular structures.

Rich<sup>20</sup> was a pioneer in such pathological studies. He found lesions resembling those of periarteritis nodosa in patients who had died at Johns Hopkins Hospital of serum sickness following sulfonamide therapy. More recently he<sup>21</sup> has pointed out 32 fatal cases in that hospital with similar diagnoses occurring since the advent of the sulfonamides, in contrast to 6 such deaths during all previous years. Gregory and Rich<sup>22</sup> have produced comparable lesions in animals by the injection of egg albumin, and Selye<sup>23</sup> by inoculation of hormone extracts and later by exposure to cold.<sup>24</sup> From the diversity of stimuli that can produce characteristic lesions similar to those found in diseases known to be aller-

gic, it seems evident that an antigen-antibody mechanism is not always essential. Furthermore, similar types of histologic lesions have been described in diseases not considered to have more than a bowing acquaintance with clinical allergy. Among these are disseminated lupus erythematosus, scleroderma, dermatomyositis, Loeffler's syndrome, rheumatic fever and rheumatoid arthritis. Klemperer,<sup>25</sup> in a recent review of this subject, agrees that whereas certain pathologic lesions characterized by collagen swelling and vascular damage are highly characteristic and their presence suggests allergy as a possible cause, they are not specific for the allergic response and are therefore not of diagnostic clinical value.

Periarteritis nodosa has stimulated interest not only from the pathological but also from the clinical standpoint. Elkeles<sup>6</sup> emphasizes the conception that this disease may be an extreme degree of vascular allergy and likewise calls attention to the great variety in the clinical picture including fever of the remittent type, tachycardia, polyneuritis, polymyositis, albuminuria, cylindruria, hypertension, blood eosinophilia and asthmatic attacks with bronchitis. Contratto<sup>27</sup> described 2 cases, 1 in a man with active pulmonary tuberculosis in whom, at different times, biopsies of the lymph nodes showed first periarteritis and later tuberculosis. Bergstrand<sup>28</sup> accents the morphologic similarity between periarteritis nodosa and the transitory infiltration of the lungs in Loeffler's syndrome. Two cases of this disease are presented by Alpper<sup>29</sup>, ragweed-pollen sensitivity was considered to be the etiologic factor in 1. The other, in an asthmatic patient, was characterized by two successive and recent attacks and one probable attack four years previously. Henderson and Pierce<sup>30</sup> have stressed the transitory nature of the focal pulmonary lesions in this disease as demonstrated by serial x-ray films. Tropical eosinophilia falls in the same group. It is important that this disease may be relieved, as in Irwin's<sup>31</sup> 2 cases, by treatment with arsenicals.

#### HISTAMINE AND ANTIHISTAMINIC DRUGS

The greatest clinical advance in allergy in recent years has been provided by the antihistaminic drugs. Their development is an outgrowth of inquiries into the role of histamine in allergy. These studies were initiated in 1910 by Dale and Laidlaw,<sup>32</sup> who noted the similarity of the action of histamine and the manifestations of anaphylactic shock in animals. On the basis of the histamine theory, various efforts have been made within the past decade to counteract the effects of this drug. The first of these was by attempted desensitization with repeated injections of histamine. This was followed by a wide use of histamine azoprotein "hapamine" with the hope that a conjugate might stimulate antibodies more easily than treatment with histamine itself. Histaminase was next offered



as a possible means of destroying histamine, but this enzyme failed in vivo to live up to its promises in vitro. None of these methods of treatment have been accepted with more than limited enthusiasm. The antihistaminic drugs provide a different approach to the problem, they have a competitive chemical action against histamine. Loew,<sup>33, 34</sup> in reviews of the pharmacology of these compounds, states that their effectiveness appears to be definitely related to their ability to diminish or block the

TABLE 1 Disorders Alleviated by Histamine Antagonists, in Order of Their Susceptibility to Benadryl and Pyribenzamine\*

DISORDER	BENADRYL		PYRIBENZAMINE	
	PATIENTS TREATED	PATIENTS IMPROVED	PATIENTS TREATED	PATIENTS IMPROVED
		%		%
Serum disease	5	100	1	100
Overdose reactions	4	100	25	92
Dermographia	6	100	46	83
Allergic rhinitis, extrinsic non-seasonal	6	100	144	72
Urticaria, acute	135	95	250	85
Urticaria, chronic	261	87	266	79
Dermatitis, contact	18	78		
Rhinitis seasonal (hay fever)	320	77	558	78
Dermatitis, eczematous and miscellaneous	23	74†	31	45
Physical allergy	7	71	10	70
Ménière's syndrome	13	69†	5	20
Headache, histamine and other types	14	64	8	50
Rhinitis intrinsic † allergic	183	59	399	58
Dermatitis, atopic	76	58	119	61
Asthma intrinsic, † allergic	210	53†	294	32
Asthma, seasonal	53	49	42	45
Migraine	38	45	6	17
Asthma nonseasonal, extrinsic	23	39	70	49
Pruritus	40	20	26	61

\*Adapted from Loveless.<sup>44</sup>  
†Some of the diagnostic data were inadequate to determine whether the patient belonged to the intrinsic or to the nonseasonal, extrinsic class.  
‡Suggested superiority over the other drug.

effects of histamine upon vascular and visceral smooth muscle and permeability of capillaries. He concludes that none of the evidence suggests that these drugs influence the antigen-antibody reaction. Rose<sup>35</sup> postulates that patients with allergic diseases demonstrating histamine effects must have two operative factors. The first is that the tissues must be hypersensitive to histamine, and the second that there must be a shift of this substance from the intracellular or inactive form to the extracellular or free state and that small amounts of histamine may thus be continually released, producing local effects, and then rapidly removed from the blood by means of the kidneys. Feinberg and his associates<sup>36-42</sup> have been pioneers in reviewing the experimental and therapeutic status of the antihistaminic drugs. Reports of clinical results with the most widely known of these medications, benadryl and pyribenzamine, have now been recorded in several thousand cases. Such accounts include the percentage effectiveness of either or both drugs in various conditions, their comparative merits and the frequency of their side reactions. Carefully controlled series of over 100 cases in each study have been published by

Feinberg et al, Henderson and Rose,<sup>43</sup> Blumenthal and Rosenberg,<sup>44</sup> Wagner,<sup>45</sup> Arbesman and his co-workers,<sup>46, 47</sup> the American Academy of Allergy,<sup>48</sup> Loveless and Brown,<sup>49</sup> Waldbott,<sup>50</sup> O'Leary and Farber,<sup>51</sup> Levin<sup>52</sup> and Todd.<sup>53</sup>

Loveless,<sup>54</sup> in a recent comparative study based upon a survey of twenty-six clinical reports from the literature, summarizes the results of trials in over 2000 cases with pyribenzamine and in nearly 1500 with benadryl, as well as a percentage tabulation of side reactions (Tables 1 and 2).

It is obvious from these tables and from compilations by other reviewers<sup>17, 36</sup> that benadryl and pyribenzamine provide temporary relief in varying degrees for many types of allergic manifestations. It is equally evident that side reactions are common. These are usually transient in nature and are seldom serious or of more than temporary concern either to the patient or to the physician. Occasionally, however, more serious reactions occur. Epstein<sup>55</sup> reported the development of eruptions in 2 patients with atopic eczema while they were taking pyribenzamine. One eruption was of the eczematoid type, the other resembled

TABLE 2 Side Reactions to Benadryl and Pyribenzamine\*

SIDE EFFECT	BENADRYL	PYRIBENZAMINE
	INCIDENCE	INCIDENCE
	%	%
Sedation	45.0	8.5
Disorder of central or peripheral nervous system	10.0	3.0
Gastrointestinal complaints	8.0	9.0
Dizziness or vertigo	7.0	3.0
Numbness of lips and tongue	6.0	1.0
Exhaustion	4.5	2.0
Vascular	3.0	1.0
Muscular pain or inco-ordination	1.5	1.0
Hypersensitiveness	1.0	1.0
Miscellaneous	0.2	0.3
Headache	0.0	2.5

\*Adapted from Loveless.<sup>54</sup>

pityriasis rosea. Both cleared with the withdrawal of the drug and recurred on its readministration. Blanton and Owens<sup>56</sup> recorded the appearance of agranulocytosis in a seventy-three-year-old woman after eight weeks of therapy for urticaria with pyribenzamine. After withdrawal of the drug and treatment with penicillin, the blood and clinical pictures returned to normal. Urinary incontinence, involuntary spastic movements of the extremities, slurred speech and irrational behavior were noted by Weil<sup>57</sup> in a boy of three and a half after two doses of 50 mg of Benadryl and a third of 100 mg six hours later. Sternberg<sup>58</sup> describes a twenty-two-year-old nurse who was hospitalized for hysteria after one week's treatment with daily doses of 200 mg of benadryl. On withdrawal of the drug she became normal. Geiger, Rosenfield and Hartman<sup>59</sup> reported palpitation, dimmed vision, malaise, drowsiness, heartburn and nausea after a daily total dose of 300 mg of benadryl given over a three-

day period. After the next dose of 50 mg, the patient was found unconscious. All symptoms subsided with withdrawal of the drug. With the exception of the unconsciousness, they all recurred when the same dosage of benadryl was administered a week later. The dangers of self-medication are illustrated by Borman,<sup>50</sup> who recounts the case of an eighteen-year-old girl who obtained excellent relief of hay fever and asthma from her first day's treatment with two 50-mg benadryl capsules. Encouraged to increase her own dose, she took forty capsules (2000 mg) within the following three days. She became drowsy and irrational but with forced fluids completely recovered within forty-eight hours. It was believed that her judgment may well have been affected by the first two capsules of benadryl.

I recently observed the following case, as yet unreported.

A 25-year-old housewife, referred for study of chronic vasomotor rhinitis, had previously been given 200 mg of pyribenzamine daily for treatment of persistent nasal obstruction. She was apparently normal in other respects. During the first 10 days of this medication she obtained relief from the nasal symptoms but became increasingly nervous, sleepless, absent minded and depressed. She even contemplated suicide. At times she forgot how to cook or how to set the table. She also neglected now and then to feed her children or to get her husband's dinner upon his return in the evening. She lost 14 pounds in 10 days. On the 11th evening of medication, her husband entered the kitchen to find the patient finishing the last of a new bottle of twenty-five 50-mg pyribenzamine tablets purchased that day. Her physician was on vacation but another doctor was called. He prescribed an emetic, with resultant evacuation of the stomach contents. During the next few days the psychotic symptoms gradually disappeared and at the end of a week the patient felt perfectly normal except for nasal obstruction which had recurred. She therefore decided to resume the pyribenzamine in doses of 200 mg daily. All the former symptoms slowly returned. Five days later she was visiting one of her children sick in the hospital when the child's physician arrived to find the mother sound asleep at her daughter's bedside. Pyribenzamine was immediately stopped with a gradual return to normal. With the reappearance of nasal obstruction, a 5-day trial was given to theophylline, one of the newer antihistaminics, which was prescribed in amounts of two tablets daily. This therapy was followed by sustained exhilaration and a feeling as if the patient were walking on air or flying. Reduction of the dose to one tablet did not improve the situation so that this medication was discontinued, with final disappearance of the untoward symptoms.

The satisfactory clinical response to the earlier antihistaminic drugs such as benadryl and pyribenzamine, as well as the obvious disadvantages of their side actions, has prompted much investigation in an effort to obtain more powerful but less toxic products. The trade names of over thirty such antihistaminic substances are already a matter of record. A number of these are having extensive therapeutic trial. Reports have appeared upon clinical results with neo-antergan,<sup>51</sup> antistine<sup>52</sup> and decapryn.<sup>53</sup> Halpern<sup>54</sup> has been working on the thiodiphenylamine derivatives, of which 3015 RP and 3277 RP are the most promising. This new chemical series is reputed to be less toxic and more active than earlier ones. It is too early to evaluate

these or the many other antihistaminic drugs that will appear upon the market within the near future.

As Feinberg,<sup>55</sup> Burrage<sup>56</sup> and others<sup>57</sup> have stressed, the histamine antagonists are valuable adjuncts to the treatment of allergic disease, but they do not immunize the patient, nor is their benefit more than a brief one. It is obvious that their administration is attended by frequent side effects of varying degrees of severity. Not enough time has elapsed to rule out the possibility of more remote toxic effects.

#### EMOTIONAL FACTORS

In any large group of patients with allergic manifestations the etiologic factors remain obscure in a considerable percentage even at the end of routine allergic studies. Mitchell et al.,<sup>58</sup> bothered by this common observation, analyzed a group of 600 consecutive cases of representative types of allergy. This series was divided into positive skin reactors whose symptoms such as hay fever and extrinsic asthma could be correlated with proved causative factors and non-reactors with perennial vasomotor rhinitis, "intrinsic" asthma and chronic urticaria. Early age of onset was evident in the reactor group in contrast to a late beginning of symptoms in the other. This in itself is not unusual, since many observers, including Rackemann,<sup>59</sup> have pointed out that asthma starting before the age of thirty is a different disease from that which begins after forty. In the nonreactor group, there was a 2:1 predominance of females with symptoms most common in the third, fourth and fifth decades — a time in life in which the authors considered conflict and situational factors to be related to the production and persistence of allergic symptoms. Subsequently, 1129 cases of perennial asthma observed over a ten-year period were classified according to the major etiologic factors. It was found that 1 out of every 5 of these cases (22.7 per cent) were diagnostic and therapeutic failures. One hundred such year-round cases were next selected for careful individual review, and it was again discovered that approximately the same number (21 per cent) showed signs of psychologic maladjustment in view of the expressions of confusion, hostility, fear, guilt and so forth that were brought out in prolonged and careful history taking. These characteristics were in sharp contrast to the clear-cut, succinct, unemotional statements common in the reactor groups. Gleebe and Kerr<sup>61</sup> presented 4 such cases in detail, illustrating the importance of psychogenic elements in 1 case of chronic headache, in 1 of chronic urticaria and in 2 of primarily intrinsic asthma. They agreed with the previous authors that the role of the emotions in causing, precipitating and aggravating latent allergic sensitization will be adequately recognized and that the study, diagnosis, treatment and relief of allergic manifestations will be substantially furthered if

history taking is broadened to include psychologic events, particularly if these events are correlated with the somatic reactions at the time of occurrence. Mitchell and Curran<sup>69</sup> have reviewed the earlier literature and stressed again the advisability of the sensitive, nondirect method of approach to this type of patient rather than one of abrupt questioning. This technic has seemed in numerous cases to reveal useful psychologic data, with the production of a state of release and attendant psychologic adjustment and symptomatic improvement.

Henderson<sup>70</sup> believes that asthma should be conceived of primarily as an organic disease based on disturbed respiratory physiology—the result of allergic influences—in which psychic and emotional factors may indeed be important in precipitating, modifying or inhibiting attacks in patients already the subjects of asthma. Billings<sup>71</sup> discusses 12 patients with bronchial asthma from the psychogenic standpoint. He warns that the establishment of such an etiology requires relatively long psychotherapeutic guidance and that the more diffuse the complaints, the less satisfactory the therapeutic results are likely to be. Cormia<sup>72</sup> has classified the psychosomatic dermatoses, including such disorders of allergic interest as urticaria, dermatographism, pruritus and atopic and contact dermatitis. He outlines a combined dermatologic and psychiatric approach, which he believes lends itself well to all but the more long-standing recalcitrant conditions for which prolonged psychoanalysis is indicated. Metzger<sup>73</sup> recognizes the importance of the emotions and discusses a case. Fabricant<sup>74</sup> deliberately induced fright and emotional upsets in 3 susceptible subjects during determination of the nasal reaction, with a resultant rapid shift from slightly acid (pH 6.5) to alkaline (pH 7.3). A similar type of observation was made by Wolff,<sup>75</sup> who noted vasoconstriction of the nasal mucous membranes of a boy when he was frightened. Nasal congestion appeared, however, when fear disappeared and rage took its place. MacLean,<sup>76</sup> and Swanton,<sup>77</sup> both in Australia, have presented cases to illustrate the psychophysical interreactions in the asthmatic patient. Although Salter<sup>78</sup> emphasized the importance of the psychogenic factor in asthma almost seventy years ago and many observers are now willing to agree to its possible role in allergy, comparatively few papers have appeared upon the subject up to recent years, and even fewer large series of cases have been carefully studied from this angle. I believe that in no case should psychologic study replace but rather that it should more frequently supplement other generally accepted methods of allergic investigation. I predict, moreover, that there will be a wider acceptance of the importance of this approach in certain types of allergic disease.

## CONCLUSIONS

The field of allergy has now become so broad that its concepts must be integrated with those of the fundamental medical sciences as well as with those of its parent internal medicine. The skin test has ceased to be the only trade-mark of the allergist. Advances in allergy are often initiated, developed and reported in other fields. Progress in allergy can no longer be reviewed in its entirety.

The modern role of pathology in allergy is illustrative of this modern trend. Recent pathological studies suggest a common histologic denominator between diseases now known to be allergic and several conditions with similar histology but with no clinical characteristics of allergy. Future investigations may point the way to some common causative mechanism in these diseases.

A review of the antihistaminic drugs records a definite advance in allergic therapy. Caution is advised that their administration be carefully supervised, and it is recommended that they be employed to supplement rather than to replace well tried principles of allergic management.

The psychologic approach to the etiology of otherwise unexplained allergic disease marks another step forward. A broader acceptance of this diagnostic and therapeutic aid to allergy is urged and predicted for the future.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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#### CASE 34221

##### PRESENTATION OF CASE

A sixty-two-year-old electrician entered the hospital complaining of malaise and exhaustion.

Five days before admission he noted abdominal rumbling and loose stools. He felt that he was about to have an attack of diarrhea. He went to the basement in the dark to take a drink of whisky to relieve this and by mistake picked up a bottle of carbon tetrachloride and drank about an ounce. As soon as he tasted it he spat it out and induced vomiting with his finger. He vomited numerous times during the following several hours and also had repeated watery stools. Later that evening he felt better although somewhat weak. He slept well but on the following morning was so weak that he stayed home from work. During the following two days he continued to have severe anorexia, taking very little food or drink. In addition, he noted an intermittent, dull, aching pain in the lower back, "between the hips," and soreness in the right upper quadrant. His wife noticed that his eyes were bloodshot and the surrounding tissues swollen. The urinary output decreased to little more than a few drops each day. During the twenty-four hours preceding entry all symptoms seemed to decrease in severity. He felt somewhat stronger, and the pain in the back diminished. He passed about an ounce of normal-looking urine during this twenty-four-hour period. There had been no jaundice, chills, fever or hematuria.

The past history revealed an attack of acute nephritis at the age of twenty-two, necessitating eight weeks of convalescence at home. There had apparently been no residua. There was no known albuminuria or hypertension. The patient denied excessive alcoholic intake.

Physical examination revealed a well developed, slightly obese, restless man in no acute distress. There was a peculiar odor to the breath, which was described as being neither characteristically uremic nor mousy. The periorbital tissues and conjunctivas were edematous and hemorrhagic. The optic fundi were not remarkable. There was no icterus of the skin or scleras. The lungs were clear, and the

heart was of normal size without murmurs. The liver edge, which was smooth, soft and moderately tender, was palpated two or three fingerbreadths below the costal margin. There was percussion tenderness over both costovertebral angles. The extremities were normal.

The temperature was 98.6°F, the pulse 80, and the respirations 25. The blood pressure was 165 systolic, 90 diastolic.

The urine was cloudy and gave a ++++ test for albumin, the specific gravity on two specimens was 1.010. The sediment contained 20 to 30 white cells and 15 to 20 red cells per high-power field. In addition, 6 to 8 epithelial cells, loaded with fat droplets, and occasionally large granular casts were seen. The red-cell count was 4,320,000, and the white-cell count 8700, with 72 per cent neutrophils. A stool was negative for occult blood. The non-protein nitrogen was 250 mg per 100 cc. The prothrombin time was 27 seconds (normal, 15 seconds).

The patient seemed to do fairly well in spite of the fact that he voided only 75 cc of urine during the first hospital day. During the second and third days his condition deteriorated, and he gradually became drowsy. Though he passed 360 cc of urine on the third day, the urinary output dropped again on the fourth to 240 cc. Moist rales developed at the right base. On the fifth day there was an acute onset of severe dyspnea, restlessness and disorientation, which continued for two hours. Finally convulsive and twitching movements of the trunk and extremities appeared, and the patient died.

##### DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: "He went to the basement in the dark to take a drink of whisky and by mistake picked up a bottle of carbon tetrachloride and drank about an ounce." It is a source of wonder to me that it is stated that this man was not an alcoholic even though he went to the dark cellar to get a drink of whisky and drank a whole ounce of carbon tetrachloride before he tasted it.

DR. WILLIAM W. BECKMAN: The patient took whisky for medicinal purposes whenever he was ill, he kept the bottle in the basement.

DR. AUB: I suspect that he often anticipated that he was going to have diarrhea.

The soreness in the right upper quadrant is important. Carbon tetrachloride affects the kidneys and liver, and yet that is the only note in relation to the liver soreness.

This case is typical of death from carbon tetrachloride poisoning. There is no use considering anything else. In my opinion this man died of carbon tetrachloride poisoning. Why on the tenth day, I do not know. There are cases in the literature in which the patient died on the tenth day, and this is earlier than death occurring from bichloride of mercury. The difference, I suppose, lies in the fact that carbon

tetrachloride poisoning involves the liver as well as the kidneys. Though there is very little evidence that the liver was involved in this case, one should be very suspicious of it. There are not an enormous number of deaths from carbon tetrachloride poisoning recorded in the literature. Carbon tetrachloride is not a very hazardous industrial solvent. It can be breathed in fairly high concentration without damage because most of it comes out by the lungs. Many of the deaths are due to swallowing of the poison. They follow the use of carbon tetrachloride as an anthelmintic in doses of 2 or 3 or at most 4 cc. As a result of such medication a fair amount of jaundice develops, with acute yellow atrophy and death. Such a course has occurred in people who are alcoholics or who drink alcohol with the carbon tetrachloride, and in people who take a good deal of fat the fat escorting the carbon tetrachloride across the intestinal tract. There are a sufficient number of deaths from carbon tetrachloride to cause it to be avoided as a drug. The deaths that occur are characteristic of that in the case under discussion, except that most of the patients have had jaundice. This patient did not have jaundice. Anne Minot\* who worked with us on lead poisoning, found that lethal doses did not kill a dog if calcium gluconate was given intravenously. Calcium and glucose relieve the strain on the liver sufficiently so that the animal did not die when this was given. Most of the animals that did die in her series died from bleeding in the gastrointestinal tract. This patient had no evidence of bleeding, but the dogs in the experiments died of hemorrhage, through either acute ulceration or duodenal ulcer. Carbon tetrachloride causes injury to both the liver and the kidney. The liver is affected mostly at the inside center of the lobule, the outside of the lobule being less involved. This patient showed an enlarged liver and an elevated prothrombin time, but no jaundice. Is autopsy going to show any abnormality? In spite of the fact that he said that he went to the cellar because he did not feel well, he probably consumed a fair amount of alcohol, and I guess that the carbon tetrachloride did him more damage because of the alcoholic habits. On the basis of that, I think that he had a moderate amount of cirrhosis and a moderate amount of acute yellow atrophy. There is no good evidence for such a statement except that he had an enormously high nonprotein nitrogen. I should like to know what the amino acid content of the plasma was. I assume that the determination was not made.

Dr. BECKMAN: No, it was not.

Dr. AUB: If the patient had acute yellow atrophy, the best evidence would have been elevation of amino acids in the blood stream as well as jaundice. Without those data one cannot make the diagnosis of acute yellow atrophy. On the basis of pain in the right upper quadrant and the large liver, and since

carbon tetrachloride usually affects the liver, I shall say that he had a certain amount of liver destruction and acute yellow atrophy, not enough to give jaundice, and that it did not cause his death.

The chief cause of death was injury to the kidneys, which had been previously damaged. Not infrequently carbon tetrachloride affects the kidney as well as the liver, therefore, I expect to find damage to the tubules, severe damage, with acute nephritis, with uremia, convulsions and death. Some edema was probably found in the lungs, particularly the right lower base, which was said to have rales due to the fact although the record does not say so, that he was given much intravenous saline solution and got rid of very little of it by the kidney. I do not believe that caused the edema in the lungs, but it added to it. He died of uremia and, therefore, had convulsions. Why these patients get convulsions previous to death, I do not know. All the cases that I have seen as well as those in the literature have shown that I think that is probably a uremic manifestation. Carbon tetrachloride goes wherever there is fat, and yet there is very little present in the central nervous system. Fatty cells in the kidney are not unusual, because, since the drug is a fat solvent, fat gets free, and the plasma is very apt to be lipemic in this condition. It is one of the ways of knowing whether the carbon tetrachloride is doing damage.

Therapy is not usually discussed at these meetings. I think that most people do not pay enough attention to Anne Minot's suggestion of injection of calcium salts for the liver damage of carbon tetrachloride poisoning. Any patient who has acute yellow atrophy ought to be given calcium and also ought to have glucose, which is very saving of the liver in liver damage. These patients also sustain severe kidney damage. If they survive, they show a surprisingly small residue of kidney damage. The only way I know of saving them is by flooding them with fluid (a course that I suppose was followed in the case under discussion) and also by giving them an adequate amount of alkali to produce diuresis. I am glad that there is no time for further discussion because a number of people would disagree with me. But in my experience, with toxic injury to the kidney, patients do well if large quantities of alkalies are given to produce diuresis. I have seen a number of patients with bichloride poisoning who finally urinated when given large amounts of sodium bicarbonate in intravenous injections. If these people can urinate and get over the uremia, a number of them recover with surprisingly small deleterious effect on the kidneys.

Dr. TRACY B. MALLORY: Dr. Aub has made the diagnosis seem obvious. Has anyone any questions, or does anyone take exception to that diagnosis?

Mr. WILLIAM Kiyasu: What is the antidote for carbon tetrachloride poisoning — lavage?

\*Alliot A. S. Mechanism of hypoproteinemia produced by  $\text{CCl}_4$  in a dog. Carbon tetrachloride poisoning. It is relieved by calcium medication. *J. Pharmacol. & Exper. Therap.* 43:295-315, 1911.

DR AUB After the drug has been swallowed, I suppose so. It is absorbed very rapidly, being a lipid solvent. I suppose that a stomach wash is indicated, but that does not help much unless done very promptly. Even after repeated vomiting, enough of the drug may still be retained to do damage. In bichloride of mercury, for instance, enough will be retained even after the patient has vomited continuously for an hour. I think the stomach should be washed, but castor oil or alcohol, which might further help the absorption, should not be given.

DR BECKMAN All I can say is that this emphasizes the value of these exercises, because when I had this patient on the ward as nearly as I could tell he had swallowed no carbon tetrachloride at all, but I am obliged now to admit that he must have. I stood out against the whole field, including the patient, on the diagnosis of carbon tetrachloride poisoning.

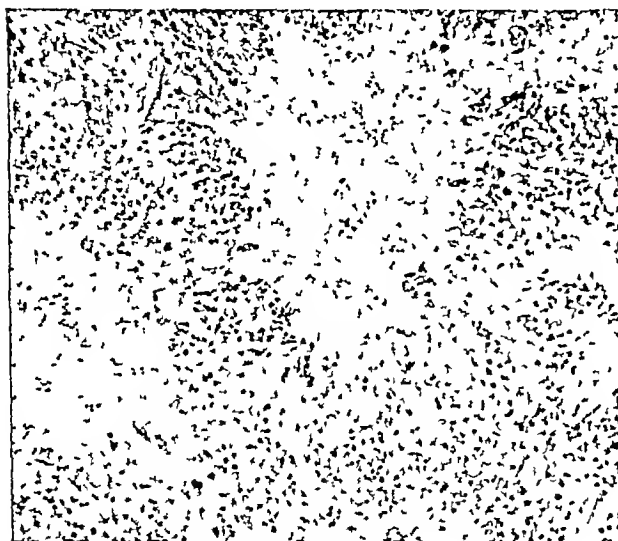


FIGURE 1

I thought that it was an exacerbation of the nephritis that he had had forty years previously and that he had developed high blood pressure and severe uremia of which he died. But I think that I was wrong.

#### CLINICAL DIAGNOSIS

Acute nephritis

#### DR AUB'S DIAGNOSES

Carbon tetrachloride poisoning, with renal and hepatic damage

Uremia

Pulmonary edema

#### ANATOMICAL DIAGNOSES

*Carbon tetrachloride intoxication*

Lower-nephron nephrosis

Central necrosis of liver, acute

Pulmonary atelectasis, both lower lobes

Arteriosclerosis, generalized, moderate

#### PATHOLOGICAL DISCUSSION

DR MALLORY The autopsy findings to my mind conclusively proved that Dr Aub was correct. The



FIGURE 2

first view of the liver was almost conclusive, and at post-mortem examination I was struck with the appearance of the liver. It was rather small, and its surface was yellow, with closely sprinkled, bright-

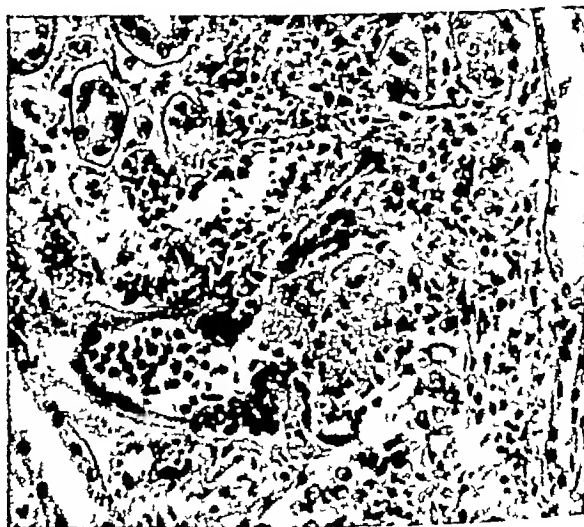


FIGURE 3

red dots. On cut surface the central half of every lobule was depressed and red. The microscopical sections showed complete loss of the liver cells in the central half or two thirds of the lobule (Fig 1). At

the periphery many of the surviving liver cells showed fat vacuoles, another phenomenon characteristic of carbon tetrachloride poisoning. The portal areas, in contrast, were quite normal and showed no cellular infiltration such as one sees in hepatitis.

The kidneys revealed a pigment nephrosis indistinguishable from that of transfusion reaction, which is what one characteristically sees in carbon tetrachloride poisoning. The picture differs from bichloride poisoning, in which the proximal convoluted tubules are injured. Here the straight tubules of the medulla are filled with hemoglobinuric casts (Fig. 2). The cortex showed dilated proximal tubules, but no cellular degeneration, and, incidentally, fat stains of the kidneys did not show any fat. On the other hand, the distal convoluted tubules disclosed a severe grade of degeneration. Figure 3 demonstrates one of the phenomena that we see characteristically in the lower-nephron lesion—a tubule, the wall of which has been destroyed, and there is a cast in process of extension into the stroma, producing a foreign-body type of granuloma in the stroma. The entire picture is like that of a kidney injured by transfusion, crush or sulfonamides. The combination of such a renal lesion with the liver lesion is very unusual in anything except carbon tetrachloride poisoning. In the Army there were a considerable number of cases of this sort that could be surely attributed to carbon tetrachloride injury. Not infrequently the renal symptoms predominated so far over the hepatic symptoms that the latter passed unnoticed.

**DR. AUB.** If the patient could have weathered the acute illness, what would the end result of the kidney lesion have been?

**DR. MALLORY.** I believe that there would have been absolute restitution to normal. There are not a great many anatomic observations on record. Kinney observed a case at the Peter Bent Brigham Hospital last year in which the patient died of homologous serum jaundice after three months, having successfully weathered a transfusion reaction in the course of which he had renal insufficiency. That kidney, so far as could be determined anatomically, was normal. There are a fair number of patients who survive a lower-nephron lesion who have been studied functionally. Those kidneys re-establish normal function in approximately two to four months.

## CASE 34222

### PRESENTATION OF CASE

A fifty-five-year-old Finnish woman entered the hospital because of loss of weight, easy fatigability and the appearance of an abdominal mass, which was gradually increasing in size.

About three months before entry the patient began to lose her appetite and to feel tired. During this

period she lost about 25 pounds in weight. Two months before entry she first noticed the appearance of a mass in the abdomen. She claimed that the mass had increased considerably in size since that time. One week prior to admission she began to vomit after the ingestion of any foods or liquids. This had persisted at intervals until entry. The bowel movements had been regular until several days before admission, at which time she had several bouts of nonbloody diarrhea four to six times daily. On the day of entry the bowel movements were normal. She had never had any abdominal pain, and the mass had not been tender.

Thirty-one years before entry she had an operation for a "dropped stomach," and thirteen years previously, while she was in Finland, a hysterectomy was performed. She had two children, aged sixteen and twenty-five years, both were living and well.

The only positive physical finding was the presence of a firm irregular mass (20 by 15 cm.) located mainly in the left midabdomen but extending for a short distance to the right of the midline beneath the umbilicus. The lower border of the mass projected into the pelvis on the left side. It was freely movable and nontender. The abdominal wall was flaccid, and it was possible to pick up the tumor and move it several centimeters in any direction. The greatest mobility was from side to side. Pelvic examination revealed no masses in either vault. The uterus was absent. The lower border of the tumor on bimanual examination could be felt at the pelvic brim, more prominently on the left.

The temperature, pulse, and respirations were normal. The blood pressure was 142 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 11.8 gm. and a white-cell count of 7800, with 83 per cent neutrophils, 5 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils and 3 per cent basophils. The platelets were normal. The nonprotein nitrogen was 26 mg. per 100 cc.

A barium enema was done on the second hospital day. The colon filled readily without evidence of obstruction. There were numerous small diverticula scattered throughout the sigmoid. A tumor mass was observed in the left side of the abdomen. It compressed the left side of the transverse colon but did not appear to be attached to the colon. The remainder of the colon showed no abnormality. The cecum was freely movable, and the terminal ileum filled readily and appeared normal. The findings were consistent with a mass extrinsic to the large bowel.

On the third hospital day an exploratory laparotomy was performed.

### DIFFERENTIAL DIAGNOSIS

**DR. MARSHALL K. BARTLETT.** In summary, this is the problem of a fifty-three-year-old woman with a three months' history of loss of appetite, weight loss (25 pounds) and a mass in the abdomen of at



least two months' duration, which had increased in size during that time. A week prior to entry she began to have vomiting and intermittent diarrhea. The only helpful physical finding on admission was the presence of a firm, irregular and quite movable mass.

May we see the x-ray films?

DR. STANLEY M. WYMAN: These are two films from the barium examination of the colon. The transverse colon is unusually low in position. This film shows compression of the left transverse colon without definite involvement of the mucosa. There is a suggestion of faint outlining of the mass in this position. It lies higher than I thought from the description. Diverticula are present in the sigmoid. The terminal ileum is not well seen. I can see no other masses, and there is no evidence of calcification in this area.

DR. BARTLETT: Can you tell whether it is above or below the transverse colon?

DR. WYMAN: It seems to be above.

DR. BARTLETT: Can you see the kidney shadow and the spleen?

DR. WYMAN: The left kidney shadow can be seen at this point. The lower pole is outlined well. The upper pole cannot be seen. The spleen is outlined and seems to be within normal limits in size and shape. The liver is not remarkable. The right kidney is probably essentially normal.

DR. BARTLETT: That really helps me somewhat, because it rules out certain diseases that I had thought of considering, not having seen the x-ray films and not knowing whether the tumor was above or below the transverse colon. They fairly well rule out the possibility that this was an ovarian cyst, which if present, should have been below the transverse colon. There are various other things against that possibility. I think it would be unlikely that an ovarian cyst would cause nausea and weight loss and gastrointestinal symptoms, unless it was a malignant cyst with extensive metastases, and of course the pelvic examination does not give any hint that this was connected with the pelvic organs. In spite of the fact that a hysterectomy had been performed, the ovaries could have been left behind. We have no information about that. All in all, a cyst of the ovary seems like a remote possibility.

The normal shadow of the spleen, I think, is adequate to rule out the possibility that this was a tumor of the spleen. Such a tumor arising in the

spleen would probably displace the colon differently. Again, it hardly is enough to account for the weight loss and gastrointestinal symptoms on that basis. Along the same line of reasoning, I will exclude the kidney although Dr. Wyman is not quite sure about the kidney.

DR. WYMAN: I think that the lower pole is all right.

DR. BARTLETT: That is even more helpful. I shall rule out the possibility of kidney disease. An intravenous pyelogram, of course, would give further evidence on that point, but I take it that the kidney was not seriously considered as the source of this woman's trouble or such an examination would have been done. I dwelt at some length in my mind on that possibility because I had recently been caught at a conference at another hospital on a pelvic tumor that I thought was an ovarian cyst and it proved to be a solitary cyst in an ectopic pelvic kidney.

What other possibilities are there? I thought about the possibility of a lesion in the mesentery of the small bowel, but, again, a tumor in that region would not lie above the transverse colon, it would be below it. I shall dismiss it. Anything that I might say about a cyst or tumor in the mesentery of the small bowel can be equally well applied to the large bowel—to the transverse colon—and we might consider that possibility. There are tumors of the colon that attain considerable size. I am thinking of spindle-cell tumors, which become relatively large without causing much in the way of symptoms. There are two general types based on the point of origin: those that arise in the submucosal areas and the ones that tend to invade the lumen and cause obstruction. I feel sure that one would not attain this size and still give a negative barium enema or a barium enema that shows no evidence of obstruction. The subserous type may get big before symptoms appear. They are apt to manifest themselves by bleeding. We have no particular evidence, other than a moderately reduced hemoglobin, that this patient had bled. There was no history of massive hemorrhage by rectum. No examination of the stool is recorded, but there is nothing particular to suggest that she bled by rectum.

How about a cyst of the mesentery of the transverse colon? I think that is a possibility. Those cysts are rare. When they occur they may either be lymphatic in origin or they may be dermoids. They occasionally can be as big as the mass in this case, but not very frequently. I do not believe that all

these lesions would have been described exactly like this one, which was an irregular, firm mass. I think that a cyst of the mesentery of the transverse colon should be smooth. Again, with a cyst in the mesentery of the bowel or even with a subserous tumor arising from the transverse colon, it is rather difficult to account for the anorexia, the weight loss and the other symptoms.

That brings me down to the pancreas. Was this a lesion arising in the pancreas? In favor of that it seems to me, is the fact that pancreatic tumors are notorious for insidious onset, with nausea and weight loss, and perhaps this case would be best explained by something of that type. What kind of lesion of the pancreas would resemble this? I think it was too big for a solid tumor of the pancreas. I do not remember seeing or hearing of a solid tumor of this size behaving in this fashion, because they usually produce more symptoms before they reach this size. How about a cyst of the pancreas? There are various types of cysts. The most common is probably the so-called pseudo-cyst, which is the end result of an inflammatory process or sometimes is the result of trauma. These tumors attain good size, and they lie really extrinsic to the pancreas. They start in but extend outside the substance of the pancreas, so that a pseudo-cyst could be in this location and present this picture on physical examination. These cysts, however, are ordinarily unilocular and smooth on the external surface. Likewise, retention cysts, which presumably result from occlusion of some part of the ductile system of the pancreas, are smooth and do not reach this size. If this was a cyst of the pancreas, it seems most likely that it was a cystadenoma. These cysts are multilocular, so that the external surface is irregular, they attain considerable size, often are benign in the early phase and often become malignant as they progress and grow larger. Such a cyst may be present in various locations. Above the lesser curvature, between it and the liver, is the most common place. The next most common is between the greater curvature of the stomach and the transverse colon, which is where this tumor seems to have been located. The least common point is below the transverse colon, though the cysts can even be present there.

It seems to me, considering the various facts that we have, that a lesion of the pancreas is probably the best diagnosis that I can make. Of the various possible lesions of the pancreas, I think a cystadenoma is probably the most likely.

DR. TRACY B. MALLORY: I am surprised that someone does not try to connect the patient's nationality with the lesion.

DR. BARTLETT: What was her nationality?

DR. MALLORY: Finnish. I knew that we had had an echinococcus cyst not long ago, and as I read over the history, that was my guess, but unfortunately I was not correct.

#### CLINICAL DIAGNOSIS

Ovarian tumor?

Tumor of stomach?

#### DR. BARTLETT'S DIAGNOSIS

Cystadenoma of pancreas

#### ANATOMICAL DIAGNOSIS

*Malignant lymphoma, giant-follicle type, of mesentery of small bowel*

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: The preoperative diagnosis was probable tumor of the stomach, but I gather that the surgeons were very uncertain about it. The patient was explored. The ovaries and stomach were both found to be perfectly normal. There was a large mass in the root of the mesentery of the small bowel, which had grown outward at one spot along the mesentery to a point where it involved the wall of a short segment of small bowel. The tumor went rather far posteriorly, but the surgeons were able to feel the kidney and were sure that it was not connected with that. The mass as a whole was impossible to resect, but the small segment of involved ileum was resected, since it was feared that the bowel might soon become obstructed. At operation frozen section was attempted, but it was not possible to say what the tumor was. Our later section showed it to be malignant lymphoma, giant-follicle type, and the patient is now having x-ray treatment.

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## THE NOLAN-MILES BILL IN RETROSPECT

AFTER much publicity and rather more than the usual amount of misstatement and raucous vituperation from its opponents, the Nolan-Miles Bill has been referred to a legislative research committee for "further study" (*sic*). This is discouraging to those who have worked long and hard for the passage of this sensible piece of legislation. Perhaps the best the medical profession can do is to review the situation and see what can be done in the future.

There are two classes of opponents to this bill. One consists of a rather small minority of sincere but misguided people. To change the opinion of this group seems an impossible task, even though the evidence is overwhelmingly in favor of the value

of the bill to humanity and to medical research. If this small group had represented the only opponents there would have been no great difficulty in obtaining favorable action. But there is a much larger and a far more vocal group that advances no reasons against the bill other than those of misguided sentimentality. Unfortunately, this group does not confine itself either to facts or to the real purpose of the bill as explained in its wording. These opponents harp continually on the cruel doctor whose sole interest in the passage of this bill is to steal, torture and eventually kill the pet dog of little Willie Jones. They disregard entirely the present laws for the disposal of lost animals, ignoring the fact that annually thousands of animals are put away in a humane manner because no one claims them at the pounds. It is these animals, which are to be destroyed under the law, that the proponents of the bill wish to make available for the fundamental, important and humane purposes of medical research.

W. E. Mullins, in the *Boston Herald* of March 18, has done an outstanding piece of constructive journalism in his report on the Nolan-Miles Bill. He wrote as follows:

Legislators have lost sight of the fact that the responsibility is theirs and not that of the medical profession. The politicians should vote on every bill strictly on merit and not on the noise that is made by organized minorities. Busy doctors should not be required to go several times annually to the legislature to plead for the right thing.

One of the legislators had stated in the press, (*Boston Herald*, March 15, 1948) that, "Doctors can individually advise their legislators on bills vital to the protection and progress of Massachusetts medicine — 'or risk losing them'."

As Mr. Mullins wrote:

The Massachusetts Medical Society sent its official spokesman to Beacon Hill to plead for it. This is an organization of the foremost medical men of this state. Against the considered opinion of this Society that passage is essential to the continuation of medical research, what do we have? We have this opinion: "I do not think it will help medical science."

The opinion quoted came from a physician serving in the legislature.

The Council of the Massachusetts Medical Society is a body democratically elected by the Society to voice its opinions. At a meeting held

shortly before the bill came to the legislature, the Council voted unanimously to go on record as expressing its hearty approval. What more can a legislator want as evidence of approval of the medical profession? To be sure, a vote is a vote (especially in an election year), but even if every member of the Massachusetts Medical Society appeared individually they would still be greatly outnumbered by the very vocal group of opponents. In addition to the official approval of the Council, however, the Massachusetts Medical Society sent to represent it some of the outstanding physicians and surgeons in the Commonwealth and, indeed, in the country.

The medical profession of Massachusetts made great efforts to obtain favorable action on the bill and came near to success. Disappointing and belittling as it is to be subjected to taunts and insults at a public hearing on Beacon Hill, the medical profession must nevertheless take up this added burden for the greater good of humanity and the advance of the profession. It must accept this challenge and by greater effort make its considered opinion heard, and *effectively* heard by those who, in many cases, are swayed only by the number of votes and not by the thought that goes behind a "yes" or a "no." It must do this rather than adopt a defeatist attitude, which would be welcome to its opponents.

One good, at least, has come out of the clamor of the controversy. A public education process has been started, and the need for greater and continuing education has been made apparent.

### MILLIONS FOR DEFENSE

The Council on National Emergency Medical Service of the American Medical Association sponsored in April a conference to consider the defense of America in the event of a general national emergency. Fifty-one persons were present, representing an impressive majority of the state medical societies as well as a number of national associations of allied professions.

Certain important points were brought out during the course of the conference. Such an emergency, should it occur, will apply especially to our

scattered industrial centers, and effective medical service will depend largely on strong state organizations. A resolution was accordingly adopted calling on the component societies of the American Medical Association to activate committees that will work with and under the guidance of the Council.

Such a committee, although it had not yet been activated, had already been authorized by the Council of the Massachusetts Medical Society on October 2, 1946. This action was taken at that time as a logical procedure, with no emotional implications.

Further points were elaborated at the conference in April. In the event of such a national emergency as war with a foreign power, all the available medical personnel of military age should not be called up. Recent history has shown that too many stagnant pools of manpower result from this profligate policy. Another world war would be total to a degree never yet realized, and the ratio of one physician for each fifteen hundred of population, considered sufficient in World War II, would be inadequate for the expected civilian needs. A more flexible deployment of the medical profession to serve both our forces under arms and our population under fire would have to be arranged.

The regular branches of our armed forces should forget their old school ties and give the civilian components equal rank and consideration with their professional military personnel. In past wars it has been a rare honor for a civilian physician, however well equipped, to attain the rank of brigadier general. Furthermore, and this seems almost axiomatic, no emergency should be allowed to disrupt completely the continuity of medical progress and education. The possibility of a national future even after another war should not be entirely disregarded.

Certainly our minds must be kept open for the consideration of wholly new problems in this coldly scientific age. If war should come a new group of special weapons consisting of chemical agents, biologic products and releases of atomic energy with far reaching effects in both time and space will be available and might be employed. The medical profession will be of transcendent importance in

the event of such a disaster, and none of its value must be canceled out by outworn procedure or by antiquated customs of military regimentation. The chief obligation of civilized man, however, is to prevent, by the most forceful measures that can be undertaken, the catastrophe attendant on the opening of such a Pandora's box. In the contemplation of these weapons we are considering the zenith of military power. In a hypothetical fourth world war, as Einstein has mildly reminded us, man will perhaps revert to rocks as the only available missiles.

A combination of the wisest minds and the strongest hands must guide the future of the world. Their efforts must be directed toward the salvation and not the degradation of mankind. They must prepare for prevention, they must arm to keep the peace. The only fear permissible, as we have been told before, is that of fear itself.

Toynbee has shown that the civilization in control of its own destiny is that in which the creative minority remains actively in quest of moral and not of material gains. Our new, free, western civilization is still of that fiber. Its people are they that "shall mount up with wings as eagles, they shall run and not be weary, and they shall walk and not faint."

## VENEREAL-DISEASE CONTROL

A RECENT release from the Office of the Surgeon General reports a remarkable drop in the incidence of venereal disease during 1947.<sup>1</sup> For the Army as a whole, the decrease amounted to 40 per cent, for soldiers stationed in the United States, it was more than 50 per cent. This is an encouraging note in view of the trend toward increased rate in the civilian population as recently reported.<sup>2</sup> The Surgeon General credits this accomplishment to a new approach on the part of the Army, based on "an intelligent appeal to the higher moral sense of the individual," with "moral, spiritual, psychological, as well as objective factors." In this program the reasons for good conduct are stressed through group and individual education and conferences. Programs of activity and planned entertainment

help to maintain the interest of the soldier and to steer him away from sources of trouble when he is off duty. This approach has supplanted prior concepts, which emphasized the aspects of prevention, with the implication that the soldier was not remiss so long as his illicit relations did not result in infection. Training films used during the war have been replaced by new films reflecting the current trend, dramatizing "The rewards of good conduct as well as the effect of social diseases on an individual's future health and happiness."

Such a creditable accomplishment is certainly praiseworthy, and it is to be hoped that the rates of venereal disease among civilians will also be reduced. The statistical reports of the United States Public Health Service for the fiscal year 1947 show a rate 2 per cent less in the civilian population of the continental United States than had been predicted.<sup>3</sup> This is still a higher incidence than that of the preceding year. There is usually some degree of parallelism between military and civilian disease, but during periods of peace, the incidence of venereal disease in the general population is not likely to drop so much as the military rate.

A moral and spiritual approach is more likely to be effective in the absence of hostilities. The possibility of impending death that engenders a certain amount of reckless abandon and fatalism is bound to arise in the minds of troops in time of war. This factor complicates the moral aspect of the situation. Nevertheless, an education campaign in time of peace may well lay the foundation for better future success in the control of venereal disease.

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## MASSACHUSETTS MEDICAL SOCIETY DEATH

ELLIS — Frederick W. Ellis, M.D., of Newton Centre, died on April 30. He was in his ninety-second year.

Dr. Ellis received his degree from Harvard Medical School in 1881. He was a fellow of the American Medical Association and the American Association for the Advancement of Science. He was the last surviving founding member of the American Physiological Society.

A son, Dr. Laurence B. Ellis, of Newton Centre, survives.

## A HUNDRED YEARS AGO

Within the circle of benevolent institutions, in this or other countries, there cannot be found a parallel to the one in the City of Boston organized expressly for poor, destitute, sick children. This is truly a charity which is not puffed up and which vaunteth not itself. It seeks no great names upon a circular, to give it importance, carries no contribution box into the church, makes no appeals to the pockets of the benevolently disposed, nor in any way seeks the applause of men. Quietly, without ostentation, without parade, but with a steady purpose, it feeds the hungry, clothes the naked, nurses the sick, and takes care of helpless little children. This is charity indeed, and of which our favored city, aye, and the world may be proud. — Notwithstanding the activity of the press in the United States, the question has been appropriately asked, what is the present state, and what are the future prospects, of the medical literature of this country? There is no dearth of authors. Originality of thought and boldness in execution are characteristics in the practice of American physicians and surgeons. Various institutions vie with each other in developing the resources of a science that investigates the laws of our being, and ameliorates the sufferings to which humanity is incident. New and striking exhibitions of mental effort, in all the various branches of medical study, are being made — and it is morally certain, that a few years will serve to bring out results that will redound to the advancing influence of the medical literature of the Union and place it on a foundation as firm and glorious as the government whose broad mantle covers and protects the whole. — By our exchanges we perceive that the various medical institutions of the country will be generally represented in the approaching meeting of the American Medical Association. The Counsellors of the Medical Society of Massachusetts have appointed fifty delegates. At that rate, throughout the country, the number of the whole will be great indeed. — A difficulty has existed in bringing within the embrace of the Massachusetts Medical Society all the well-qualified physicians of the Commonwealth. Some have not liked the payment, it is averred, of an annual tax of three dollars — particularly those who are located so far from the business center of the Society, Boston, as to make it expensive, and not always convenient, to attend, and such, believing that they could not receive an equivalent for their money, in becoming members, have wholly declined all connection. Others, who are excellent, stable-minded, staunch friends, and have exerted themselves to uphold the character of the Society, with veteran determination, have found themselves at times in embarrassment in not being able to consult with a practitioner who does not belong to the Society — a certain by-law

forbidding them to do so. All this has been discussed over and over again in the Council. It is confidently expected that alterations soon to be proposed will meet the cordial concurrence of all parts of the State, and that harmony, prosperity, influence and usefulness will follow their adoption. — Our colleagues in Buffalo, understanding that two Harvard students are at each other's throats for the honor of discovery of *Colloidal* — or what is termed in Buffalo the "new Boston notion" — hope that its parentage will be settled with less discussion and ink-shed than in the instance of the Ictheon. — Dr. Charles A. Greene of Millbury reports having seen last summer in Western New York, a young woman who had but three fecal discharges in nine years. She has but little physical strength. Her heart beats like an infant's, her respiration is peculiar, and so slight is the effort that it is hardly distinguished by a careful observer. There has been an attempt on the part of the physicians in her neighborhood to remove the underlying difficulty (whether it be a partial stricture of some part of the intestines, or a want of action in them, is unknown) but in vain. Oliver in his *Physiology*, makes mention of some persons having no discharge in one year, but no instance like the above has he ever found recorded. — Dr. T. J. W. Pray of Dover, New Hampshire reports the case of a Mr. Thompson, 35 years old, long subject to fits of intoxication. For five days previous to examination he had been in a beastly state of inebriation, and indeed it was found, upon inquiry, that he had drank in that time two gallons of "West India rum." At the expiration of the fifth day he wished medical aid. He seemed not to require any active medical treatment but rather the expectant plan, and he was depleted a very little for an experiment. The blood was forthwith drawn, and it was found destitute, in a measure, of its watery elements — alcohol having been substituted therefor. Immediately a lighted taper was applied to it, and it began to burn with a flame similar to that of alcohol. The fact that the blood did burn was substantiated by various respectable citizens of South Berwick who were eye-witnesses at the time the blood was drawn, and saw the experiment tried. The conflagration produced such an effect upon the patient that he refrained from his intemperate habits, and afterwards became a more sober man. — At the meeting of the American Medical Association in Baltimore, Dr. Holmes of Boston, of the Committee on Medical Literature, read a lengthy report, and very amusing withal. The report embraced a rather scathing review of American Medical Literature. The doctor was employed nearly two hours in reading it. It was laid upon the table. — The Annual Meeting of the Massachusetts Medical Society, which is the most interesting medical convention in New England occurs on the last Wednesday in May. At 10 o'clock A. M., the members assemble at the

Masonic Temple, Tremont Street, for the transaction of business. After the election of its Counsellors, and the delivery of a discourse by Dr L V Bell, they will dine together at Faneuil Hall, the renowned cradle of liberty — Extracted from the *Boston Medical and Surgical Journal*, April-May, 1848

R F

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The June schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows

CLINIC	DATE	CLINIC CONSULTANT
Salem	June 7	Paul W Hugenberger
Haverhill	June 9	William T Green
Brockton	June 10	George W Van Gorder
Lowell	June 11	Albert H Brewster
Greenfield	June 14	Charles L Sturdevant
Springfield	June 15	Garry deN Hough, Jr
Pittsfield	June 16	Frank A Slowick
Worcester	June 18	John W O'Meara
Hyannis	June 24	Paul L Norton
Fall River	June 28	David S Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

## MISCELLANY

### BOSTON LYING-IN HOSPITAL

Mr Richard D Mills has been appointed administrator by the trustees of the Boston Lying-in Hospital. Mr Mills, who served as a supply officer during the war, has been administrative assistant at the University Hospitals, Cleveland, and, since 1946, administrator of the Suburban General Hospital, Bellevue, Pittsburgh.

## CORRESPONDENCE

### SPONTANEOUS PNEUMOTHORAX

*To the Editor* The article by Dr Ralph M Myerson entitled "Spontaneous Pneumothorax," which appeared in the April 1 issue of the *Journal*, recalls a personal experience with this condition that may be of educational interest. While stationed with the United States Army in Bavaria, Germany, I was privileged to attend 2 cases and heard of a third case of spontaneous pneumothorax occurring in apparently healthy persons. All patients were young men — 2 American and 1 German. Each occurred while the patient was sking in the nearby Alps and was not, so far as could be determined, related to any falls or mishaps that accompany participation in this sport. Subsequent disposition of the 2 cases observed made follow-up studies impossible, but thorough examination at the time, aside from positive x-ray findings of the pneumothorax, failed to reveal any underlying or previous lung disease. An inquiry of a German physician indicated that such an occurrence is not too uncommon in the non-indigenous or inexperienced skier coming to that mountain area.

In view of the above experience two points arise for consideration. A rarely considered factor in the precipitation of spontaneous pneumothorax is described. Spontaneous pneumothorax in apparently healthy persons resulting from the decreased atmospheric pressure associated with airplane ascents and altitude-chamber studies is known to occur. That an inherent weakness in the pleura or the presence

of a superficial pleural bleb is a prerequisite is generally assumed in all cases of spontaneous idiopathic pneumothorax. In addition to the hyperventilation and increased depth of respiration attending a decrease in atmospheric pressure, sking superimposes the strain of strenuous exercise and motion of the arms and chest. This exertion may have been the only factor in the cases cited. But the fact that 2 of the cases and probably the third definitely occurred in apparently healthy persons under identical conditions implies that atmospheric pressure had a strong contributory effect. Secondly, it would be of interest to compare the incidence of spontaneous pneumothorax in healthy persons subjected to unaccustomed altitude variations similar to that in the cases cited above. Thus far, knowledge only extends to the influence of atmosphere under passive conditions. It may be necessary to make some revision in the statistics pertaining to this condition regarding both over all frequency and the particular locale studied.

THOMAS F FRAWLEY, M D

Buffalo, New York

## BOOK REVIEWS

*Reading and Visual Fatigue* By Leonard Carmichael, Ph D, and Walter F Dcarbhorn, M D, Ph D. 8°, cloth, 483 pp, with 103 illustrations and 6 tables. Boston: Houghton Mifflin Company, 1947. \$5.00.

This book presents an excellent review of the literature on reading and visual fatigue, as well as the results of extensive new experimentation on these subjects conducted by the authors' associates. The Committee on Scientific Aids to Learning made financial grants to Harvard University and Tufts College to undertake the studies presented.

The first half of the book reviews in some detail the literature on visual fatigue and reading, the problem of illumination, blinking and the recording of eye movements. The second half describes experiments in which 40 high school and college students read for periods as long as six hours. During the reading continuous recordings were taken, providing an electroencephalogram, a horizontal electrooculogram, a vertical electrooculogram, an electrocardiogram and a record of page turns. The instrumentation appears to have been excellent, and the statistical analysis competent.

The results of the investigation support the modern view that "eye strain" is of central origin. The authors make the following statement:

The most important fact about reading for long periods as shown by the laborious recording and statistical techniques of these experiments is not a specific change in physiological mechanism. It is not a change in eye muscles, for example. Rather, the basic variable which seems to determine the presence or absence of changes during work done in long periods of time and which can be described as "fatigue" is a general characteristic of the subject's whole attitude toward his task.

The eye muscles are so much more powerful than is necessary for even prolonged reading that "the first index of fatigue seems to come in the alterations of the general attitudes and general feelings of the subject, not in a breakdown of the sensory-neuromuscular mechanism which actually performs the task."

The book should be of particular interest to all who are concerned with visual education.

*Stereoscopic Atlas of Neuroanatomy* By H S Rubenstein, M D, Ph D, and C L Davis, M D. 4°, boxed, 19 pp, and 43 stereoscopic plates. New York: Grune and Stratton, 1947. \$10.00.

This atlas was designed primarily for the use of students and physicians taking a refresher course in brain anatomy. It consists of forty-three single plates, and a small pamphlet, comprising a dissection manual and an index to the plates. Each plate has a lettered localization diagram in addition to the photographic reproduction of brain structure. The artwork is good, and the atlas should prove valuable to interested persons.

(Notices on page 222)

# NOTICES

## ANNOUNCEMENT

Dr. Edward J. Ferrarone announces the opening of his office at 289 State Street, Springfield for the practice of orthopedic surgery

## NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, June 3, at 7:15 p.m. in the classroom of the Nurses' Residence. The subject "Obstetric Cases" will be discussed by Dr. Marjorie Woodman. Dr. R. Adelaide Draper will be chairman

## NEW ENGLAND PEDIATRIC SOCIETY

The spring meeting of the New England Pediatric Society will be held in New Haven, Connecticut, on Wednesday, June 9

### PROGRAM

At New Haven Hospital (789 Howard Avenue)

- 12 m. to 1 p.m. Pediatric Conference
- 1 to 2 p.m. Luncheon
- 2 to 4:30 p.m. Scientific Program

At New Haven Medical Association (364 Whitney Avenue)

- 5 to 6 p.m. Social Hour
- 6 p.m. Dinner
- 7 p.m. Multiple Birth in Colonial Times. Dr. Ernest J. Caulfield, of Hartford, Connecticut.

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 3

### THURSDAY JUNE 3

- 7:15 p.m. Monthly Clinical Conference and Staff Meeting. New England Hospital for Women and Children

### FRIDAY JUNE 4

- \*10:00 a.m.-12:00 m. Medical Staff Round. Peter Bent Brigham Hospital

### TUESDAY JUNE 8

- \*12:15-1:15 p.m. Clinico-orthopedic Conference. Peter Bent Brigham Hospital
- \*1:30-2:30 p.m. Pediatric Rounds. Burroughs Memorial Hospital for Children. Massachusetts General Hospital

### WEDNESDAY JUNE 9

- 12:00 m. New England Pediatric Society. New Haven Hospital and New Haven Medical Association Headquarters.
- \*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital
- \*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater. Children's Hospital

\*Open to the medical profession

- May 17-29. American Surgical Association. Page 455, issue of March 25.
- June 2. Children's Hospital Alumni Association. Page 648, issue of April 29.
- June 3-6. New England Hospital for Women and Children. Notice above.
- June 3-6. American Orthopedic Association. Page 614, issue of May 6.
- June 7-10. National Gastroenterological Association. Page 455, issue of March 25.
- June 8. New England Society of Anesthesiologists. Page 734, issue of May 20.
- June 9. New England Pediatric Society. Notice above.
- June 11. Harvard Medical School Class of 1898. Page 722, issue of May 15.
- June 14-16. American Neurological Association. Page 582, issue of April 15.
- June 16-18. New England Health Institute. Page 754, issue of May 20.
- June 17-20. American College of Chest Physicians. Page 455, issue of March 25.
- June 20. American College of Radiology. Page 722, issue of May 13.
- June 20. National Conference of County Medical Society Officers. Page 754, issue of May 20.
- June 20 and 21. American Radiology Society. Page 543, issue of April 8.
- June 21 and 22. American Society for the Study of Sterility. Page 381, issue of March 11.
- June 22. University of Pennsylvania Medical Alumni Society. Page 678, issue of May 6.
- June 25 and 26. Christian Medical Society. Page 492, issue of April 1.
- June 28-30. American Academy of Pediatrics. Hotel Schroeder, Milwaukee, Wisconsin.
- July 6-14. Students' International Clinical Congress. Page 455, issue of March 25.
- July 12-17. First International Polio-myelitis Conference. Page 36, issue of January 1.

- AUGUST 11-21. International Congress on Mental Health. Page 344, issue of March 4.
- AUGUST 23-26. International Society of Hematology. Page 419, issue of March 18.
- AUGUST 26-28. American Association of Blood Banks. Page 420, issue of March 18.
- SEPTEMBER 7-11. American Congress of Physical Medicine. Page 582, issue of April 15.
- SEPTEMBER 13-15. American Academy of Pediatrics. Olympic Hotel, Seattle, Washington.
- SEPTEMBER 20-25. American Hospital Association. Page 310, issue of February 6.
- SEPTEMBER 29. Mississippi Valley Medical Editors Association. Page 170, issue of January 29.
- OCTOBER 6-9. American Board of Ophthalmology. Page 170, issue of January 29.
- NOVEMBER 1-3. American Clinical and Climatological Association. Page 382, issue of April 15.
- NOVEMBER 8-12. American Public Health Association. Page 470, issue of April 15.
- NOVEMBER 10-13. Association of Military Surgeons of the United States. Page 722, issue of May 13.
- NOVEMBER 20-23. American Academy of Pediatrics. Annual Meeting, Chalfont Hotel, Atlantic City, New Jersey.
- DECEMBER 7-9. Southern Surgical Association. Annual Meeting, Page 543, issue of April 8.

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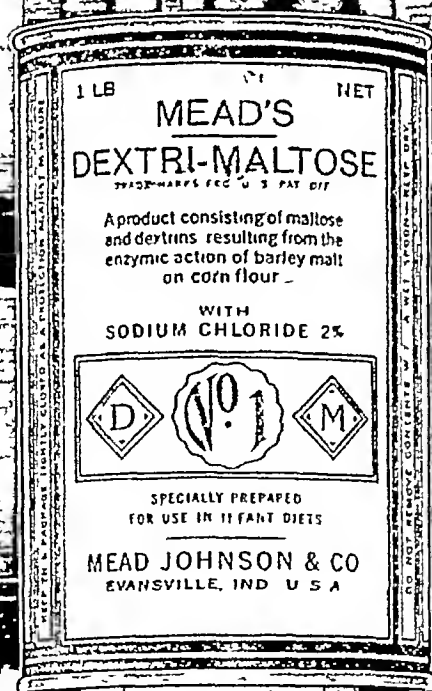
This course will deal primarily with the treatment of fractures, but the management of many other traumatic conditions will be presented — namely the physiology of bone repair, soft-tissue injuries, surgical shock, bone metabolism, burns, hand surgery, plastic surgery, vascular injuries, chest injuries, trauma in the central nervous system, bone tumors, anesthesia in traumatic conditions, the use and misuse of x-rays in the handling of fractures and physical therapy and rehabilitation

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# BACKGROUND



# The New England Journal of Medicine

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Volume 238

JUNE 3, 1948

Number 23

## TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)\*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§

ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D. ||

BOSTON

IT IS the purpose of this paper to record the results of clinical and hematologic studies on 5 children with acute leukemia treated by the intramuscular injection of a synthetic compound, 4-aminopteroylglutamic acid (aminopterin). This substance is an antagonist to folic acid regarding the growth of *Streptococcus faecalis* R.

The occurrence of what he interpreted as an "acceleration phenomenon" in the leukemic process as seen in the marrow and viscera of children with acute leukemia treated by the injection of folic acid conjugates<sup>1</sup>—pteroyltriglutamic acid (teropterin) and pteroyldiglutamic acid (diapterin)—and an experience gained from studies on folic acid deficiency suggested to Farber that folic acid antagonists might be of value in the treatment of patients with acute leukemia.<sup>2</sup> Post-mortem studies of leukemic infiltrates of the bone marrow and viscera in patients treated with folic acid conjugates were regarded by Farber as evidences of an acceleration of the leukemic processes to a degree not encountered in his experience with some 200 post-mortem examinations on children with acute leukemia not so treated. It appeared worth while, therefore, to ascertain if this acceleration phenomenon could be employed to advantage either by radiation or nitrogen mustard therapy after pre-treatment with folic acid conjugates or by the administration of antagonists to folic acid.<sup>3</sup> A series of folic acid antagonists was made available by Dr. Y. Subbarow and his colleagues.<sup>3-5</sup>

The objective data sufficient to justify research in the direction of antagonists to folic acid in the treat-

ment of leukemia were obtained from studies on a four-year-old girl with a rapidly progressing acute myelogenous leukemia. Treatment from February 17 to March 24, 1947, with pteroyldiglutamic acid (diapterin), in a dosage of 100 to 300 mg intramuscularly daily, had no effect upon the hematologic picture. The patient appeared to be moribund. A second bone-marrow biopsy on March 25 verified the diagnosis of myelogenous leukemia. Pteroylaspartic acid, the first antagonist to folic acid to be employed in our studies, was given intramuscularly from March 28 to April 4 in amounts of 40 mg daily without altering the clinical course. Post-mortem examination on April 4 revealed a markedly hypoplastic bone marrow, with a few immature cells. A change of this magnitude in such a short time has not been encountered in the marrow of leukemic children in our experience.

This observation was followed by clinical, laboratory, and post-mortem studies\*\* on a group of 14 children with acute leukemia treated with pteroylaspartic acid and on 7 treated with methylpterotic acid. The details of these observations will be reported separately.

Sufficient encouragement was obtained from these observations to justify further studies on the effect of more powerful antagonists to folic acid on the course of acute leukemia in children. Since November, 1947, when a sufficiently pure substance became available, to the time of this writing (April 15, 1948) we have made studies on 16 children with acute leukemia to whom the most powerful folic acid antagonist we have yet encountered, 4-aminopteroylglutamic acid (aminopterin††) was administered by intramuscular injection. Many of these children were moribund at the onset of therapy. Of 16 infants and children with acute leukemia treated with aminopterin 10 showed clinical, hematologic and pathologic evidences of improvement of important

\*Presented at a meeting of the Division of Laboratories and Research, The Children's Medical Center, Boston, April 8, 1948.  
†This study was supported in part under Grant No. 250 of the National Cancer Institute, United States Public Health Service, and in part under a grant from the Charles H. Hood Dairy Foundation.

‡Assistant professor of pathology, Harvard Medical School; pathologist-in-chief and chairman, Division of Laboratories and Research, The Children's Medical Center, Boston.

§Assistant professor of pediatrics, Harvard Medical School; hematologist and physician to The Children's Medical Center, Boston.

¶Research fellow in pathology and tumor research, The Children's Medical Center, Boston.

||Research fellow in pediatrics, The Children's Medical Center, Boston.

\*\*These studies were carried out by a group consisting of Sidney Farber, Gilbert G. Lent, James W. Hawley, Ernest Eichwald, Robert D. Mercer and E. Conover Pearce. ††

††This compound was synthesized by the Calco Chemical Division of the American Cyanamid Company.

nature of three months' duration at the time of this report. Six patients did not respond well, 4 of these are now dead, and 2 were unimproved. This paper presents detailed clinical, hematologic and bone-marrow studies in 5 children selected from these 10 who showed evidences of important improvement—the course in the other cases was essentially similar. The patients are selected for the purpose of illustrating some of the problems concerned with the use of aminopterin and because they demonstrate the best results that we have

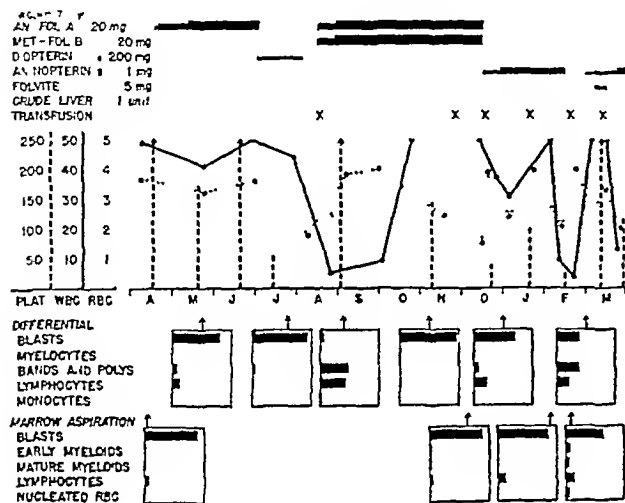


FIGURE 1 Course of Leukemia in Case 1

observed. The toxic effects are stressed in these histories, and the temporary nature of the remissions is emphasized.

### CASE REPORTS

**CASE 1** W G, a 7 1/2-year-old boy, entered the hospital for the first time on April 9, 1947, with complaints of joint pain and fever. He had been generally well until 7 weeks before admission, when pain developed in the right knee. There were no associated physical abnormalities, and the pain promptly subsided. Five days later pain recurred in the right elbow, and a low-grade fever was noted. Migratory arthralgia and fever continued until admission.

Physical examination revealed only moderate pallor and slight enlargement of the liver and spleen. The boy appeared well developed and nourished and not particularly ill.

Examination of the blood disclosed a red-cell count of 3,670,000, with a hemoglobin of 10.6 gm, and a white-cell count of 56,000, with 73 per cent blast forms. The platelet count was normal. A bone-marrow biopsy revealed leukemia.

The patient was treated with pteroylglutamic acid beginning on April 16 in doses of 20 to 60 mg daily while in the hospital, in a convalescent home, where he remained until May 20, and at home, where the injections were given by the family physician. During that time he was active and fairly well, although the white-cell count remained high and the red-cell count and hemoglobin fell slowly.

On July 1 diopterin, in a dosage of 200 mg by mouth daily, was begun. This therapy was continued for about 1 month, during which the patient steadily became more ill. The liver and spleen enlarged, and he became very anemic. The blast forms in the peripheral blood rose to 94 per cent. Joint pain and fever recurred, and by August 13 he was critically ill, with a temperature reaching 106°F. He was readmitted to

the hospital and received several transfusions. Pteroylglutamic acid and methylpterol, in doses of 40 mg each, were given intramuscularly daily. The patient was discharged after about 2 weeks, and pteroylglutamic acid and methylpterol, in doses of 20 mg each, were continued in the Tumor Therapy Office. A period of remission ensued, during which the red-cell count and platelets returned to normal levels, the liver and spleen receded in size and the nutrition improved remarkably. He returned to school part time in October and was in quite good condition. The white-cell count had risen to high levels, however, and in November general deterioration began. The liver and spleen enlarged, and he became so anemic that transfusion was necessary by November 24. Only temporary benefit resulted and transfusions were required at about 3-week intervals.

Aminopterin was started on December 16 and given daily, in doses of 0.5 mg intramuscularly, for six doses. By December 30 the white-cell count had fallen from 60,000 to 19,000. There was moderate improvement in activity and appetite. Thereafter unfavorable weather made daily visits to the clinic impossible, and 1 mg of aminopterin was given approximately three times weekly for about a month. During that time there was no striking clinical or hematologic improvement, although the patient was not seriously ill.

On February 3 daily injections of 1 mg of aminopterin were begun. A bone-marrow biopsy and aspiration revealed 85 per cent blast forms, no megakaryocytes and no erythropoiesis. After 10 days of regular therapy the white-cell count had fallen from 78,000 to 5000, but severe stomatitis made cessation of therapy imperative. Within a week without therapy, the stomatitis had healed completely, and the patient had developed a ravenous appetite. The nutrition gradually improved. By February 21 the liver was no longer palpable, and only the tip of the spleen could be felt. Bone-marrow aspiration and biopsy revealed a slight decrease in blast forms and slight erythropoietic activity. The platelets reached normal levels about 1 month after this course of daily therapy. On March 1 the white-cell count began to rise in spite of daily administration of 0.25 mg of aminopterin, and by March 6 was 75,000. The spleen again enlarged. The dosage of aminopterin was raised to 1 mg on March 8, and after about 10 days the white-cell count had fallen to 12,000. Slight stomatitis again appeared, and the dosage of aminopterin was reduced to 0.5 mg daily, with 1 unit of crude liver extract weekly. The white-cell count has remained at a high-normal level, and the spleen is again slowly receding. The stomatitis is still present but is not progressing and does not interfere with ability to eat.

The leukemia in this case progressed slowly during treatment with pteroylglutamic acid and methylpterol, but during a course of diopterin became rapidly worse (Fig 1). The liver and spleen enlarged, severe anemia developed, and the blast forms in the peripheral blood rose above 90 per cent. The patient appeared critically ill, with a maximum temperature of 106°F. Transfusions and therapy with these two folic acid antagonists were followed by a marked but temporary remission. Irregular therapy with aminopterin has been of no benefit, but on two occasions daily injections have produced good clinical and hematologic remissions. On both occasions, stomatitis has interfered with optimal use of the drug. At the time of writing the patient is in excellent physical condition.

**CASE 2** R P, a 6 1/2-year-old boy, was admitted to the hospital on March 4, 1948, with the chief complaint of increasing pallor. His growth, development and general health had been excellent until about 3 weeks before admission, when tonsillitis had developed. This had subsided promptly, but the patient had become lethargic, and increasing pallor was noted. About 10 days before admission his parents began to notice that he bruised easily.

Physical examination disclosed a well developed and fairly well nourished boy who was very pale and lethargic. Many small ecchymoses were noted over the extremities. The liver edge extended 4 cm. below the costal margin, and the tip of the spleen could be felt at the costal margin. There was slight generalized lymphadenopathy.

Examination of the blood revealed a red-cell count of 1,880,000 with a hemoglobin of 5.65 gm and platelets of 46,000 and a white-cell count of 4200, with 20 per cent immature or blast forms. A sternal marrow aspiration revealed 75 per cent blast forms. No megakaryocytes were seen.

Shortly after admission the patient developed a spiking temperature up to 104 or 105°F daily, and rapidly became more lethargic. Blood cultures revealed no growth. Frequent transfusions raised the red-cell count and hemoglobin to normal levels, but there was an unfavorable clinical response. The white-cell count fell to 1500. He appeared critically ill. On the 7th hospital day penicillin was started, and the temperature decreased although it continued to reach 101 to 102°F daily.

On the 8th hospital day, aminopterin (1 mg) and crude liver extract (1 unit) were given intramuscularly. The white cell count was 1500. This medication was continued daily and the patient rapidly became more alert and active. The white-cell count remained near 2000. He was discharged moderately improved on March 15. After discharge he was seen 6 times weekly in the Tumor Therapy Clinic and 1 mg of aminopterin and 1 unit of crude liver extract were given at each visit. Rapid improvement in appetite and activity continued. A second sternal marrow biopsy and aspiration after one week of therapy revealed a 25 per cent decrease in blast forms and an increase in more mature leukocytes and megakaryocytes. By March 25 the white-cell count had reached 5000, with 34 per cent neutrophils, 63 per cent lymphocytes and 2 per cent blast forms. His activity and appetite were normal and easy bruising was no longer a complaint. At about that time he developed minor

returned to normal and he is in school part time. The red-cell count and hemoglobin are still high, and the white-cell count is within normal limits. Immature cells or blast forms have disappeared from the peripheral blood, and the bone marrow shows a moderate shift toward maturity of leukocytes, with an increase of erythrocyte precursors and megakaryocytes. The course is demonstrated in Figure 2.

**CASE 3** G J, a 3 8/12 year-old boy was admitted to the hospital on November 2, 1947—5 days after the onset of an acute illness with sore throat and fever.

The past history and developmental history were not remarkable.

Physical examination disclosed a critically ill patient with an acute follicular tonsillitis and enlarged tender cer-

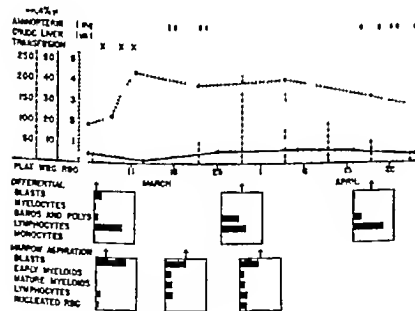


FIGURE 2 Course of Leukemia in Case 2

lesions of the oral mucosa. The dosage of aminopterin was reduced to 0.5 mg and the liver extract was given once weekly. Steady improvement has continued. The liver and spleen are no longer palpable. The patient is active in outdoor games and his endurance is good. On March 31 he returned to school where his teacher noted marked improvement in his appearance and interest. Sternal marrow aspiration on April 1 revealed a slight further reduction in blast forms, a moderate increase in megakaryocytes and a marked increase in erythropoiesis. He continues on daily injections of 0.5 mg of aminopterin with liver extract once weekly.

This patient had rapid progression of leukemia until one month after the onset, when he appeared critically ill. After three weeks of daily aminopterin therapy his activity and appearance have

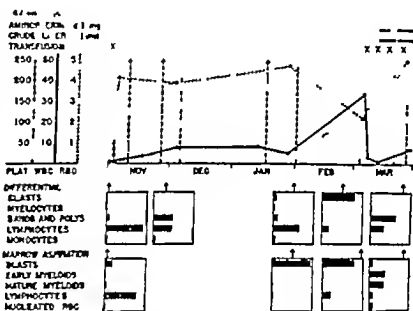


FIGURE 3 Course of Leukemia in Case 3

vical lymph nodes. There was no generalized adenopathy and no hepatomegaly or splenomegaly. A blood culture was positive for beta hemolytic streptococcus.

Examination of the peripheral blood showed a red-cell count of 1,900,000, a white-cell count of 480 and a platelet count of 123,000. Bone-marrow aspiration showed 16.4 per cent blast forms, 3.2 per cent mature polymorphonuclear leukocytes, 76.2 per cent lymphocytes and 1.6 per cent erythroid elements. On the basis of the bone marrow aspiration a diagnosis of leukemia was made. The bacteremia was treated with penicillin and streptomycin.

After recovery from the infection the patient went into a complete clinical and hematologic remission for about 2 months. The course is demonstrated in Figure 3. At that time bilateral acute otitis media developed. Two weeks later the total nucleated count of the sternal bone marrow was 910,000 (normal 200,000 to 250,000) with 96 per cent blast forms (Fig. 4A). By February 26, 1948 the white-cell count was 17,250, with 80 per cent blast forms the spleen extended to the umbilicus, petechiae began to appear, and it was obvious that the child was entering a rapidly progressive phase of the leukemia.

He was readmitted to the hospital on March 6. He appeared chronically ill with pallor, petechiae, moderate generalized lymphadenopathy and marked hepatomegaly and splenomegaly. The white-cell count, which was 30,400 with 86 per cent blast forms on admission fell rapidly to 900 by March 12, and the patient appeared moribund. Blood cultures were negative.

Aminopterin was started on March 13 in doses of 0.5 mg and given for 5 consecutive days. Crude liver extract, in a dosage of 1 unit daily, was given in the same syringe. At

the end of that time there was no noticeable clinical improvement, but the white-cell count, which was still 900, contained only 5 per cent blast forms. A sternal-marrow smear made at the end of this short period of therapy and compared to one just before therapy was started showed a shift to the right, with some reduction in blast forms and an increase in more mature forms of granulocytes, as well as a slight increase in erythroid elements. Aminopterin was discontinued until it became apparent that the leukopenia was not increasing.

After 4 days without treatment 0.5 mg of aminopterin daily, with 1 unit of crude liver extract, was given once more. The white-cell count increased gradually, and blast forms

**CASE 4** C C, a 2 1/12-year-old girl, was admitted to the hospital on August 22, 1947. Six weeks previously her father had noticed lumps about the head and neck. Two weeks previously her family physician had made a diagnosis of leukemia on the basis of a peripheral blood smear.

Physical examination revealed a pale girl, with ecchymotic areas over the lower extremities. There was marked generalized adenopathy, particularly about the parotid region, and the liver edge and tip of the spleen extended down to the iliac crests.

Examination of the blood disclosed a white-cell count of 75,000, with 80 per cent blast forms. The platelet count

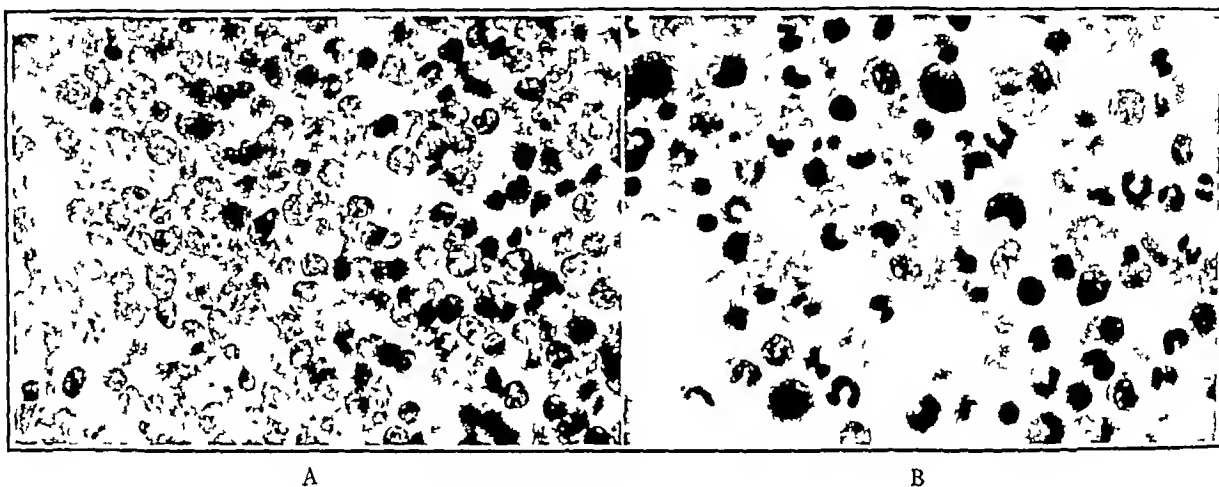


FIGURE 4 Photomicrographs of the Sternal Bone Marrow in Case 3, Showing Giemsa-Stained Section on January 29, (A) and April 3 (B), 1948 ( $\times 1000$ )

Note that the microscopical field is composed mainly of blast forms characteristic of leukemia (cell type undetermined) in the early section (A) and that a marked shift to mature cell forms, particularly of the polymorphonuclear series, with no leukemic cells, had occurred on the later examination (B)

disappeared from the peripheral blood. The child began to show clinical improvement, his appetite became better, and the liver and spleen became scarcely palpable. The petechiae and generalized adenopathy disappeared.

At the present writing there is a partial contracture of the left leg, probably resulting from leukemic infiltrations about the knee joint and in the gastrocnemius muscle. The tip of the spleen is still palpable. Otherwise the child is normal on physical examination. The white-cell count is 6700, with a normal differential. The platelet count is 152,000. Aspiration of the sternal marrow on March 29 revealed 8 per cent blast forms, with an increase in more mature granulocytes, erythrocyte precursors and megakaryocytes (Fig 4B).

This child with acute leukemia had a remission of about two months' duration after a bacteremia. At the time aminopterin was started he was in a rapidly progressive phase of the leukemia and appeared moribund. After five days of therapy there was marked improvement in the peripheral-blood and sternal-marrow picture. He has continued to demonstrate rapid and remarkable clinical improvement. Eighteen days after therapy was started the sternal-marrow aspiration showed only a slight shift toward immaturity of the myeloid elements and a moderate reduction of lymphocytes and erythroid elements. The peripheral blood at present shows slight thrombocytopenia, with a white-cell count of 8000 and a differential count that is essentially normal except for a large number of band forms.

was 54,000. The patient was discharged and given x-ray therapy to the parotid region in the outpatient department. A total of 600 r was given from September 4 to September 8. The white-cell count, which was 94,000 on September 4, had dropped to 5000 by September 11.

The patient was readmitted on September 27. She was much worse, with a poor appetite, marked pallor and massive adenopathy. The white-cell count was 1000, with 30 per cent blast forms. Several transfusions before discharge produced only slight improvement.

The third admission, on November 6, followed a generalized convulsion. The patient was comatose, with a temperature of 103.6°F.

Physical examination was essentially unchanged except that the kidneys were definitely enlarged and easily palpable. There was no positive evidence of infection. A transfusion and penicillin were given, and the patient was discharged in fair condition.

The fourth and last admission was on December 2, when there was a temperature of 105°F. There was a severe stomatitis and pharyngitis, with extensive exudation. The left ear was inflamed but not suppurating. Bronchopneumonia was present on the left. A lumbar puncture showed evidence of subarachnoid hemorrhage. A blood culture was positive for *Staphylococcus aureus*, coagulase positive.

For the first 6 hospital days the patient ran a septic temperature ranging between 105 and 103°F. She was given penicillin and sulfadiazine, as well as repeated blood transfusions, throughout the hospital stay. At this admission she was seen for the first time by the Tumor Clinic and received 20 mg of teroplerin per day for eighteen doses, from December 3 through December 20.

On several occasions the patient appeared moribund but on about the 7th hospital day she began to improve and continued to improve until the time of her discharge. The white-cell count, which had dropped to 650 on the 4th hospital day, rose to 6400 on the day before discharge. The differential count included 68 per cent neutrophils, 24 per

cent lymphocytes and 8 per cent monocytes. There were no blast forms.

After this severe infection there was a remission in the clinical and hematologic condition. During that time the patient was given an occasional dose of rotopernin to a total of 140 mg. By January 13 small lymph nodes over the scalp, parotid and cervical regions had begun to develop. These rapidly increased, and by January 19 there was massive generalized adenopathy. The peripheral blood and bone marrow continued at values approaching normal. There were only occasional to 5 per cent blast forms in the peripheral blood, with a normal total white-cell count, and 84 per cent blast forms in the bone marrow with a slight depression of mature forms and a moderate depression of erythroid forms. On January 20 aminopterin was started in doses of 1 mg daily with 20 mg of rotopernin daily. This was given on twenty six clinic visits from January 20 to February 21. Four days after treatment had been started there was a marked decrease in the size of all the lymph nodes. In 2 weeks the patient was normal on physical examination. Her appetite became very good, her disposition happy, and she began to play and run about like a normal child. Her parents stated that she was better than she had been before she became sick for the first time. Since treatment was stopped she has continued to do well. She has been without treatment since February 21 and at present is completely normal on physical examination. The total white-cell count is 9000, with an occasional blast form. The platelet count is 256,000, the red-cell count 4,600,000 and the hemoglobin 14.8 gm.

This child is known to have had acute leukemia since early in August, 1947. Her course was rapidly and progressively downhill until December, when she had a fulminating generalized infection with bacteremia. After this she had clinical and hematologic evidence of remission. In the middle of January a relapse was taking place, as evidenced by massive generalized adenopathy although the blood and bone-marrow picture remained the same. After aminopterin therapy the adenopathy disappeared. The patient has remained clinically well for forty-three days without treatment and shows an essentially normal hematologic picture at the time of writing. The course is shown in Figure 5. At the end of forty-seven days without treatment a few nodules appeared beneath the scalp and in the subcutaneous tissue over the face. It is probable that these represented leukemic deposits, although at the time of their appearance the peripheral blood was still essentially normal. Because of this finding the treatment has been reinstituted.

**CASE 5.** R. S., a 2 1/2-year-old boy, was admitted to the hospital on August 26, 1947, with the chief complaint of increasing pallor. He was one of identical twins and his birth growth and development, and general health had been unremarkable. About 10 days before admission he had developed a low-grade fever soon followed by increasing pallor, lethargy, anorexia and intermittent vomiting.

Physical examination showed a fairly well developed and well nourished and only moderately ill boy. He was very pale. There was generalized enlargement of the lymph nodes and moderate hepatomegaly and splenomegaly. X-ray study showed marked infiltration of the long bones. The hemoglobin was 5.5 gm., and the white cell count 12,400, with 41 per cent immature or blast forms.

During 2 weeks in the hospital the patient received transfusion, which restored the hemoglobin to normal levels. After discharge he was seen in the Tumor Therapy Clinic daily except Sunday and on each visit received 20 pteroylaspatic acid intramuscularly. He has been on this regime for about 2 months, during which the

progressed slowly but steadily. He became less alert and less active. He developed a limp. There was gradual weight loss, and the liver and spleen continued to enlarge. The leukocytes remained at normal levels but the percentage of blast forms increased. The red cell count and hemoglobin slowly fell, until on November 6 it was necessary to admit him to the hospital for transfusion. At that time a small pathologic fracture was noted in the left tibia. After discharge he was seen in the Tumor Therapy Office three times weekly and on each visit received 40 mg of pteroylaspatic acid intramuscularly. Late in November there was a definite acceleration in the progress of the disease. The white-cell count began to rise and the platelets fell. The patient began to bruise easily and had occasional slight oozing from the gums. He developed moderate exophthalmos. He refused to walk. Hospitalization was necessary twice in the

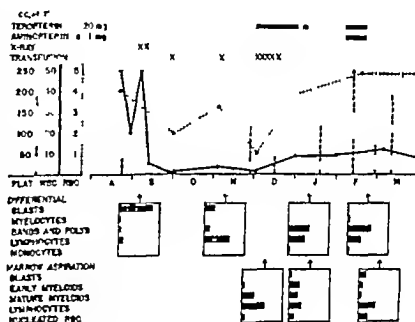


FIGURE 5 Course of Leukemia in Case 4

early weeks of December for treatment of arthritis and upper respiratory infection. Stereal marrow aspiration at that time revealed 40 per cent blast forms and little erythropoiesis. By the end of December the patient appeared moribund. He had marked generalized adenopathy, marked hepatomegaly and a spleen whose tip extended into the pelvis. There was moderate dyspnea and stridor, pallor, marked wasting and exophthalmos. There were many ecchymoses, and oozing occurred at the gingival margins.

Aminopterin therapy was begun on December 28. On each of 3 successive days the patient received 10 mg of the drug intramuscularly. During that time the white-cell count began to fall rapidly from the pretreatment level of 60,000. By December 31 the count was 9000 and respiratory difficulty was even more marked. He was admitted to the hospital. Aminopterin was discontinued and a transfusion was given. He was discharged on January 3, 1948, slightly improved but with the white-cell count only 2700. After discharge he was again followed in the Tumor Therapy Clinic. By January 13 marked clinical improvement had become apparent. The patient was walking for the first time in 2 months, and respiratory difficulty had disappeared. His appetite was ravenous. There was no more bleeding. "His clothes became loose about the abdomen." On January 27 the white-cell count reached 5000, and 0.5 mg of aminopterin was started and given three times weekly. Gradual improvement continued but a white-cell count of about 3000 persisted. In the middle of February, rotopernin in 10-mg amounts was given with each dose of aminopterin for five doses. Early in March a rise in the hemoglobin and red cell count began. Since then folic acid for a time and lately crude liver extract have been used in conjunction with aminopterin. There had been steady clinical and hematologic improvement so that at the time of writing activity, alertness and nutrition are equal to or better than those of the well tw. The liver and spleen have decreased in size, so that they are barely palpable beneath the costal margins. The red-cell and

count, differential counts and platelets are within normal limits. The sternal marrow, examined by biopsy, is normally cellular, and the differential count is normal. Erythropoiesis is active, and megakaryocytes are present in normal number.

This boy exhibited slow but regular progression of leukemia from the time of diagnosis in August, 1947, until December, when he became rapidly worse. By January, 1948, he appeared moribund. After three daily doses of 1 mg. each of aminopterin there was a rapid fall in the white-cell count, followed in about ten days by remarkable clinical improvement. On maintenance therapy there has been continued improvement until at present the

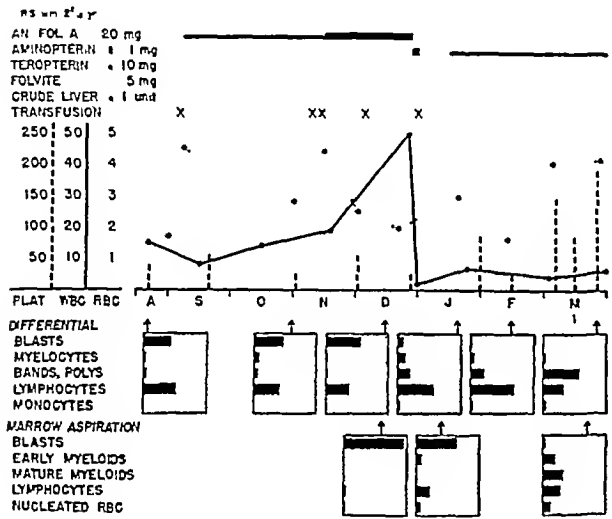


FIGURE 6 Course of Leukemia in Case 5

patient is clinically well and all the laboratory data are within normal limits. The course is demonstrated in Figure 6.

DISCUSSION

Clinical, hematologic and histologic details are given concerning 5 children with acute undifferentiated leukemia treated with aminopterin. These patients were selected from a group of 10 who responded favorably to the use of this substance. The 10 were members of a group of 16 children with acute leukemia—6 did not respond well, and of these, 4 are now dead. The observations on these patients show that the aminopterin has a marked effect upon the leukemic bone marrow and upon the immature cells in the peripheral blood, and judging from the disappearance of enlargement of the spleen, liver and lymph nodes, when those organs were enlarged, very probably on leukemic deposits in the viscera as well.

Under treatment with aminopterin the white-cell count tended to return to a normal level. This occurred in patients in whom the count was initially high and also in those in whom there was marked leukopenia at the onset of the therapy. The percentage of immature cells fell, and the blast forms decreased markedly and in some cases disappeared from the peripheral blood. The relative percentages of mature leukocytes tended to approach normal values in the peripheral blood. The peripheral-blood changes included improvement approaching the normal in the value of hemoglobin, red-cell count and platelets. Studies of the bone marrow showed changes that varied from a decrease in number to a disappearance of the leukemic cells and variation from hypoplasia to almost normal pattern. Toxic effects included stomatitis, with early ulceration. In an attempt to prevent this complication crude liver extract was employed, as were folic acid and folic acid conjugates.

This report describes only temporary remissions produced by the injection of aminopterin in children with acute leukemia. It is impossible to state whether the substance will be of value for a longer period than that covered by these studies. The toxic effects may make continued use of the drug impossible. One patient (Case 4) had been without treatment for forty-three days after having had a satisfactory remission. During this time the peripheral blood and the sternal bone marrow became essentially normal. At the end of forty-seven days without treatment a few nodules appeared beneath the scalp and in the subcutaneous tissue over the face. It is probable that these represent leukemic deposits, although at the time of their appearance the peripheral blood was still essentially normal. Because of this finding the treatment has been reinstituted. After ten days of aminopterin treatment, the nodules have disappeared once more.

These studies justify a search for other antagonists to folic acid that are less toxic than aminopterin and may be even more powerful.

SUMMARY

Clinical, hematologic and histologic details of 5 patients with acute leukemia treated with aminopterin, selected from a group of 16 patients so treated, form the basis of this paper. It is again emphasized that these remissions are temporary in character and that the substance is toxic and may be productive of even greater disturbances than have been encountered so far in our studies. No evidence has been mentioned in this report that would jus-



tify the suggestion of the term "cure" of acute leukemia in children. A promising direction for further research concerning the nature and treatment of acute leukemia in children appears to have been established by the observations reported.

Acknowledgment is made to Dr. I. Subbarow and his colleagues in the Research Division of the Lederle Laboratories (American Cyanamid Company) and their associates of the Calco Chemical Division, who are responsible for the chemical research that made possible these studies on children.

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## SARCOMA OF THE UTERUS\*

### A Report of Eighteen Cases

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ALTHOUGH sarcomas of the uterus are rare in comparison with the carcinomas of that organ, certain features of their histogenesis, pathology and clinical course make them an interesting group. Two recent cases, a sarcoma botroides and a late metastasizing leiomyosarcoma, prompted a review of the 18 cases of sarcoma of the uterus seen at the Rhode Island Hospital in the past eighteen years. Special attention has been paid to the pathology of these cases with a view to determining their probable origins and the relation of cytologic characteristics to prognosis. Observations have also been made on the clinical characteristics of the disease, with particular reference to radiation therapy. Four cases are of sufficient interest to be reported in some detail.

A brief review of the literature serves to orient one concerning the types of tumors encountered and their incidence. In 1863 Virchow<sup>1</sup> pointed out that sarcomas may arise both in the smooth muscle of the uterus and in the stromal cells of its mucosa. Geisler<sup>2</sup> noted that sarcoma constituted 2 per cent of uterine cancers, Novak and Anderson<sup>3</sup> found 4.5 per cent, and others a similar or slightly higher incidence. Piquand,<sup>4</sup> in a collective study, reported 68 cases of sarcoma of the cervix as compared with 325 of the body. Others found a much lower incidence of tumors in the cervix (Gessner<sup>5</sup> and Meyer<sup>6</sup>).

Nearly all authors report a preponderance of leiomyosarcomas over other forms of uterine sarcomas. Leiomyosarcomas may be of a very low grade of malignancy, some being classified as recurrent fibroids. Others are extremely anaplastic, widespread and rapidly fatal. Various gradations between the two extremes are to be found. Grossly, the tumors may be nodular or may grow diffusely. Polypoid projections into the endometrial cavity are not uncommon.

Stromal or mucosal cell cancers of the endometrium make up the other large group of uterine sarcomas. These are usually characterized by round cells rather than the spindle cells found in typical leiomyosarcoma. The group may be enlarged to include the various types of mixed tumors, which, in spite of their pleomorphism, presumably arise from stromal cells or their anlage. A rather confusing nomenclature has arisen for them, but, for the purposes of this paper, the following terminology is used. Mixed mesodermal tumors are those containing more than one type of tissue of mesodermal origin. Cartilage, striated muscle and myxomatous elements are most frequently encountered, but many other types of tissue have been noted. The term carcinosarcoma is used to designate tumors containing elements of connective-tissue origin and epithelium. It cannot be argued that the presence of epithelial cells sets the carcinosarcomas apart from other mixed tumors, but the term is descriptive and gives some indication of cell structure. From a careful study of the histology of the cases reported in this paper it seems likely that a large proportion of stromal-cell tumors show a mixed histology. Multiple microscopical sections may reveal small islands of cartilage or bizarre epithelial elements that are overlooked in routine observation. Thus, it was possible to reclassify several of the tumors reported below.

Two other types of rare sarcoma should be mentioned: hemangiosarcoma and sarcoma botroides. The latter is the grapelike tumor most often found in the cervical portion of infants, but also seen in adults. It presents a mixed histology, which includes epithelium, myxomatous tissue, striated muscle and, at times, a variety of other elements. This tumor is extremely malignant.

Any series of these tumors includes some that are too anaplastic to be classified. Certain others are characterized only by round cells and large num-

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bers of giant cells (Fig 1 and 2) Inasmuch as both leiomyosarcomas and stromal-cell tumors tend to form giant cells these tumors cannot always be ac-

can be distinguished It will be seen, therefore, that a mullerian-duct cell can give rise to smooth muscle, endometrial stroma or epithelium This fact may well account for the pleomorphism of some of the tumors encountered

From 1929 through February, 1947, 18 patients with sarcomas of the uterus have been treated at

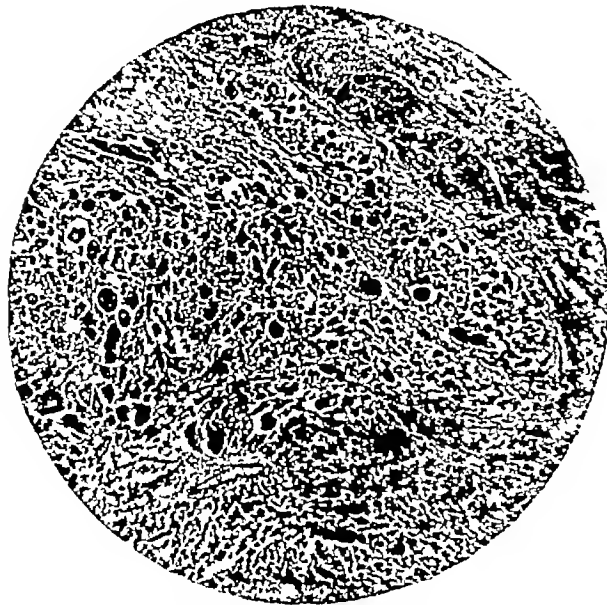


FIGURE 1 *Advancing Edge of a Predominantly Giant-Cell Tumor (Case 16)*

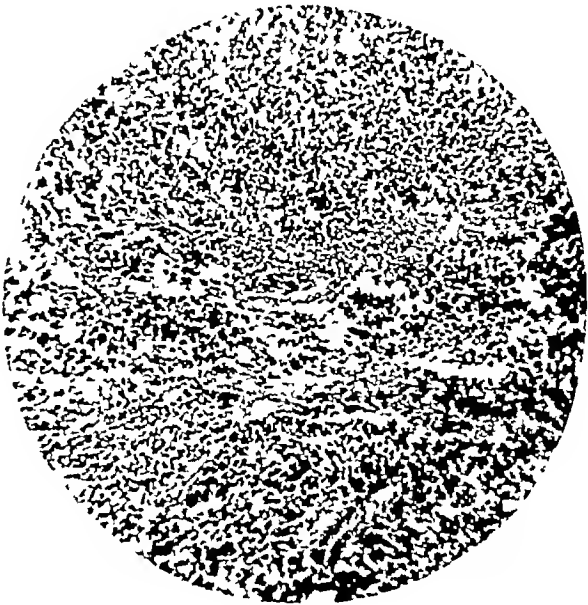


FIGURE 2 *A Few Areas Suggesting Stromal-Cell Origin from the Same Tumor As That Shown in Figure 1*

curately pigeonholed Novak and Anderson<sup>3</sup> point out that the giant cells are often evidence of degeneration of the tumor and that a diagnosis can frequently be made by a careful search for areas with few giant cells

The varied histology of the mixed types of tumors calls for some consideration of their histogenesis It

the Rhode Island Hospital These can be classified as follows leiomyosarcoma, 7 cases, mixed mesodermal sarcoma, 4 cases, carcinosarcoma, 3 cases, giant-cell (probably stromal-cell) sarcoma, 2 cases,

TABLE 1 *Results of Treatment in Patients with Leiomyosarcoma*

CASE No	AGE OF PATIENT	TREATMENT	PERIOD OF SURVIVAL	REMARKS
	yr		mo	
1	90	Panhysterectomy and bilateral salpingo-oophorectomy	3	Gross tumor not completely removed, patient died of leiomyosarcoma
2	65	Panhysterectomy and bilateral salpingo-oophorectomy	5	No recurrence of tumor patient died of chronic myocarditis
3	48	Panhysterectomy and bilateral salpingo-oophorectomy	66	Recurrence after 4½ years, patient living
4*	54	Panhysterectomy and bilateral salpingo-oophorectomy 2400 r postoperatively	8	Gross tumor not completely removed, patient died of leiomyosarcoma
5*	20	Supracervical hysterectomy	48	No recurrence, patient living
6	53	Supracervical hysterectomy and unilateral salpingo-oophorectomy, 2150 r postoperatively	6	Gross tumor not completely removed, patient died of leiomyosarcoma
7*	43	Panhysterectomy and bilateral salpingo-oophorectomy	12	No recurrence, patient living

\*These patients showed few mitoses, indicating good prognosis

will be recalled that both myometrial and endometrial elements of the uterus are derived from the müllerian ducts, which, in turn, are outpouchings of the wolffian ducts, the last being of mesodermal origin In the uterus of the 80-mm embryo (Pren-

tiss and Arey<sup>7</sup>) myometrial and endometrial layers stromal-cell sarcoma, 1 case, and sarcoma botroides, 1 case

The results of treatment in the patients with leiomyosarcoma have not been encouraging (Table 1) In 3 cases gross tumor had to be left behind at the time of operation, and all these patients were

dead within eight months. In the other cases, viewed as possible cures at the time of operation, 1 patient died in five months without evidence of recurrence, 1 developed a distant metastasis after four and a half years, and 2 are living and well one and four years, respectively, after operation.

Panhysterectomy with bilateral salpingo-oophorectomy is considered to be the treatment of choice. In Case 5 it was not done because the diagnosis of leiomyosarcoma was not made at the time of operation even though a curettage was performed. In Case 6 the cervix and surrounding tissues were intimately involved in the tumor, and the cervix was therefore left behind.

Two patients received x-ray therapy postoperatively. One (Case 4) was noted at operation to have metastatic involvement of the iliac and low aortic lymph nodes. During the first three weeks postoperatively these areas were treated with 2400 r of x-ray therapy given to each of two portals. The patient died in eight months without evidence of improvement due to radiation. In Case 6 tumor

In spite of reasonably prompt surgery after the onset of symptoms most of the patients had advanced disease when explored. One had polypoid masses filling the entire endometrial cavity, with extension to an ovary. Three others had large masses 10 cm or over in diameter, with extension outside the body of the uterus. The masses in the remaining 3 cases were 3, 4 and 5 cm in diame-

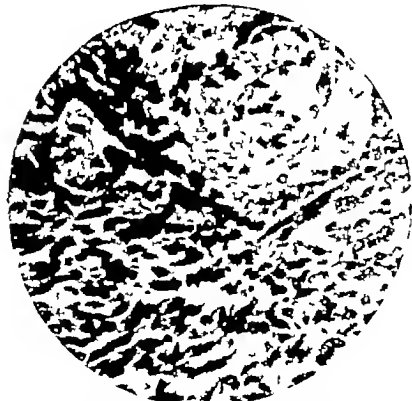


FIGURE 3 *Leiomyosarcoma in Case 7*

*This shows a relatively benign growth resembling a very cellular fibroid but lacking a capsule as it encroaches on the blood vessel above.*

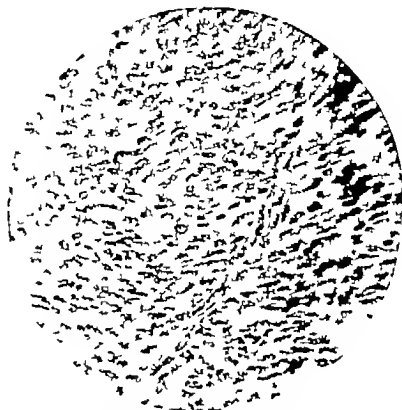


FIGURE 4 *Leiomyosarcoma with Slight Variation in Cell Morphology (Case 3)*

ter. Of these patients 2 (Cases 5 and 7) are living and well after one and four years, and another (Case 2) died of other disease in five months. This indicates that early lesions have a rather favorable prognosis.

Evans,<sup>8</sup> in a painstaking study, was able to show that the prognosis of leiomyosarcoma bears a relation to the number of mitotic figures in a given lesion. He divided his 72 cases into three groups according to the number of mitoses and found excellent results in those with no or very few mitoses per cubic millimeter. In the series reported in this paper there were 3 such cases. One patient (Case 4) had a tumor that had too great local extension for complete removal when she was first seen. Two others (Cases 5 and 7), as mentioned above, had small tumors (Fig. 3) and are living after one and four years. Presumably, tumors with few mitoses grow slowly and are discovered in many cases when still of small size.

It was also found that some of the larger tumors presented a varied histology, certain areas being much more anaplastic and widely growing than others. This suggests that sometimes areas of low-grade malignancy give rise to more rapidly growing tumor tissue with numerous mitoses (Fig. 4 and 5).

left in the region of the cervix did not respond to 2150 r given within three weeks of operation. This patient also died of the disease in six months.

On the whole these patients were operated on soon after symptoms appeared. Four had had symptoms for less than three months, 1 for three and 1 for four months, and 1 for two years.

Bleeding, pain and abdominal mass were the most frequent complaints, the major symptoms being as follows: bleeding, 2 cases, mass, 2 cases, pain, 2 cases, and bleeding, pain and mass, 1 case.

None of these tumors seemed to arise from the cervix. Only one of them was found associated with fibroids. This supports the views of Evans<sup>8</sup> and others, as opposed to the still popular concept that leiomyosarcoma arises from pre-existing leiomyoma. That such an occurrence is possible is not doubted. Indeed, Novak and Anderson<sup>3</sup> presented a photomicrograph of a leiomyosarcoma within a leiomyoma. It seems likely, how-

was performed, and a large specimen of leiomyosarcoma obtained. In the absence of other demonstrable metastasis a shoulder-girdle amputation was advised. This operation is understood to have been performed elsewhere. The patient is still living at the present writing.

This case presents several interesting aspects. The tumor did not recur clinically for four and a half years. Metastasis to bone is very rare in these tumors. Histologically, the original tumor presented many striking characteristics. Most of it was of a low grade of malignancy without mitoses (Fig. 4). Other regions presented a chaotic appearance, with numerous giant cells and vacuolated cytoplasm. This finding alone is of little note, but the presence in certain areas of numerous bizarre mitoses in association with giant cells (Fig. 5) fore-

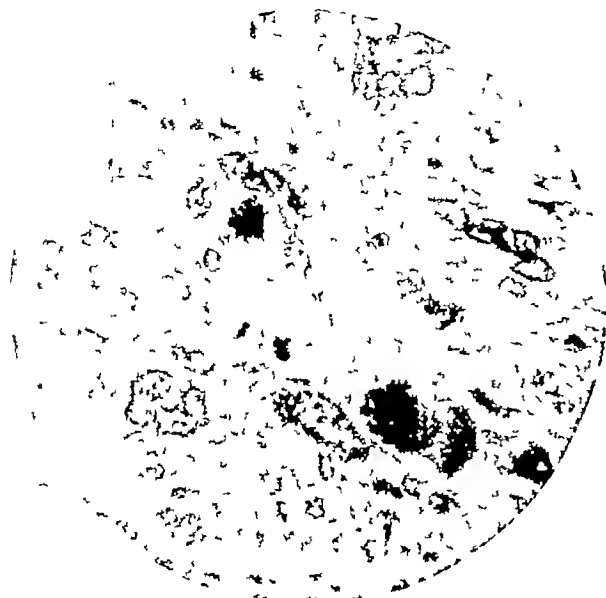


FIGURE 5 *Highly Malignant Area, with Bizarre Mitoses from the Tumor Shown in Figure 4*

ever, that most of the tumors are malignant from their inception.

The following case is presented in detail because of interesting points in the histology of the tumor, and the course of the disease.

**CASE 3** E. R., a 48-year-old woman, was admitted to the hospital on October 16, 1941, with a complaint of a low abdominal tumor of 4 months' duration.

Physical examination was not remarkable except for a mass rising out of the pelvis to the umbilicus. A preoperative diagnosis of leiomyoma of the uterus was made, and a supravaginal hysterectomy and bilateral salpingo-oophorectomy were done on October 20. The immediate postoperative course was not remarkable. A pathological diagnosis of leiomyosarcoma of the uterus extending into the left parametrium was made.

In May, 1942, the patient noted a lump in the neck, and a substernal thyroid gland containing multiple adenomas was removed.

When seen on March 11, 1946, the patient had no complaints. On her next visit, 1 year later, she stated that she had been having increasing pain in the left shoulder since the last check-up. There was a tender swelling in the region of the head of the humerus, and x-ray examination showed a cystic mass, with a pathologic fracture, expanding the upper end of the humerus (Fig. 6). The roentgenogram was consistent with a benign giant-cell tumor of bone except that the cortex was broken in places. Metastasis from cancer in the thyroid gland was suspected inasmuch as it is well known that a malignant lesion may be missed in the pathological study of apparently benign adenomas of the thyroid gland. On March 24, 1947, an aspiration biopsy of the bone tumor



FIGURE 6 *Metastatic Leiomyosarcoma of the Humerus Simulating Benign Giant-Cell Tumor of Bone (Case 3)*  
*This tumor appeared four and a half years after removal of the primary growth*

casts a poor prognosis according to Evans<sup>8</sup>. This was subsequently borne out.

Table 2 presents the pertinent data in 11 cases of stromal-cell tumors or mixed tumors of various types. Of these cases the last (Case 18) is considered separately. Of the other 10, the tumor was inoperable in 1 because of widespread disease. Four more could be treated only by exploration or partial removal of the tumor, and 1 had an inadequate follow-up study. Of the remaining 4 patients, who

were regarded as possibly cured at the time of operation, 2 had recurrence in eleven and eighteen months, and 2 are living without positive evidence of recurrence after five and thirteen years. One of these

eradicated by radiation. The patient is alive and well five years postoperatively.

Another patient (Case 14) had a much more extensive carcinosarcoma for which she received pre-

TABLE 2. *Pertinent Data in Patients with Sarcoma of Various Types*

CASE NO.	AGE	PATHOLOGICAL CLASSIFICATION OF TUMOR	TREATMENT	PERIOD OF SURVIVAL	REMARKS
8	63	Mixed mesodermal sarcoma with striated muscle	Panhysterectomy and bilateral salpingo-oophorectomy	—	Patient followed for only 2 months
9	56	Mixed mesodermal sarcoma with cartilage	Supravaginal hysterectomy	13 yr	No recurrence; patient still living.
10	68	Mixed mesodermal sarcoma with cartilage	Corectomy and radium	11 mo.	Tumor inoperable; gross tumor not completely removed; patient stated to have died of carcinoma of stomach.*
11	60	Mixed mesodermal sarcoma with myxomatous tissue	Exploratory laparotomy and biopsy	3 days	Gross tumor not completely removed; patient died of sarcoma and bronchopneumonia.
12	70	Carcinosarcoma	Radium preoperatively; par hysterectomy and bilateral salpingo-oophorectomy	5 yr	No recurrence; enlarged liver observed 1 yr after operation (possible metastases); patient living.
13	56	Carcinosarcoma	Wertheim hysterectomy and x-ray therapy for recurrence	38 mo.	Recurrence after 18 mo.; patient died of sarcoma.
14	72	Carcinosarcoma with striated muscle	X-ray therapy preoperatively; panhysterectomy and bilateral salpingo-oophorectomy	5 mo	No recurrence; patient living.
15	66	Stromal-cell sarcoma	Panhysterectomy and unilateral salpingo-oophorectomy; x-ray therapy (2412 r) postoperatively	3 mo	Gross tumor not completely removed; patient died of sarcoma.
16	51	Giant-cell sarcoma†	Radium preoperatively; exploratory laparotomy and biopsy	5 mo	Gross tumor not completely removed; patient died of sarcoma.
17	58	Giant-cell sarcoma†	Panhysterectomy and bilateral salpingo-oophorectomy	23 mo.	Recurrence after 11 mo.; patient died of sarcoma.
18	34	Sarcoma botryoides	Hysterectomy	4 mo.	No recurrence; patient living.

\*Cause of death given in city report; death may have been due to sarcoma.

†Tumor probably of stromal-cell origin.

(Case 9) had a mixed mesodermal tumor containing cartilage and lining the endometrial cavity to a depth of 2 cm. The other (Case 12) had a carcinosarcoma with a very small base in one horn of the uterus.

All these tumors lined or projected into the endometrial cavity. Some of the smaller ones assumed polypoid characteristics. Unfortunately the series is too small for any conclusions to be drawn regarding the relation of gross or microscopical findings to prognosis. It can be determined, however, that the chief cause of the low survival rate is the silent nature of many of the tumors. One of the largest, reaching to the umbilicus, caused only a distended abdomen for three days prior to hospital entry, and several other patients had equally large tumors after less than two months of symptoms.

Two patients who received preoperative radiation furnish concrete evidence of the effects of this form of therapy on the tumors. The first (Case 12), a seventy-year-old woman, was curetted, and 2450 mg. hours of radium was applied within the uterus three weeks prior to hysterectomy. The operative specimen contained three free portions of necrotic tissue, which had apparently been attached to a ragged area in one horn of the uterus. This region also presented much necrotic material. No viable tumor cells were visible in any of the routine sections. It seems fairly obvious that this was a pedunculated sarcoma and that it had been completely

operatively a total of 2190 r through each of three portals. This was given in two courses during the seven weeks before operation. In the specimen the



FIGURE 7. Carcinosarcoma (Case 13) Showing a Small Area of Carcinoma Occurring in a Predominantly Sarcomatous Tumor.

centers of the larger tumor masses were necrotic, but peripherally the tumor was widely infiltrating the myometrium.

In still another case (Case 16), 1600 mg hours of radium was applied within the uterus preoperatively. Twenty days later at laparotomy the tumor was too widespread (Fig 1 and 2) for removal to be attempted, and material was not taken for histologic study at that time. The patient in Case 10 had an inoperable pelvic mass, and the only therapy was diagnostic curettage and radium. Unfortunately the exact dosage is not given, and the effect

presented in some detail because of the previous radium and because the courses are typical of those seen in patients with similar lesions.

**CASE 9** G B, a 48-year-old woman, in September, 1924, received 1000 mg hours of radium for menopausal bleeding. Two 50-mg capsules of radium in tandem were left in the body of the uterus for 10 hours. A curettage produced insufficient material for biopsy. The patient was well until 9 years thereafter, when she began to have episodes of right-lower-quadrant pain. She reported for treatment 7 months after the onset of symptoms, when the uterus extended two fingerbreadths above the symphysis pubis. A complete hysterectomy was done on December 31, 1934, and a mixed mesodermal tumor removed with the uterus. The uterus was lined by a ragged, necrotic, friable tumor measuring up to 2 cm thick. Microscopically it was composed of undifferentiated, round cells with numerous areas of fairly well formed cartilage.

The patient was alive and well thirteen years postoperatively.

**CASE 13** A G, a 50-year-old woman, was given 1400 mg hours of radium for menopausal bleeding in January, 1937. Curettage produced endometrium diagnosed as hyperplastic. She was well from that time until May, 1943, when she was admitted to the hospital after 2½ weeks of vaginal bleeding

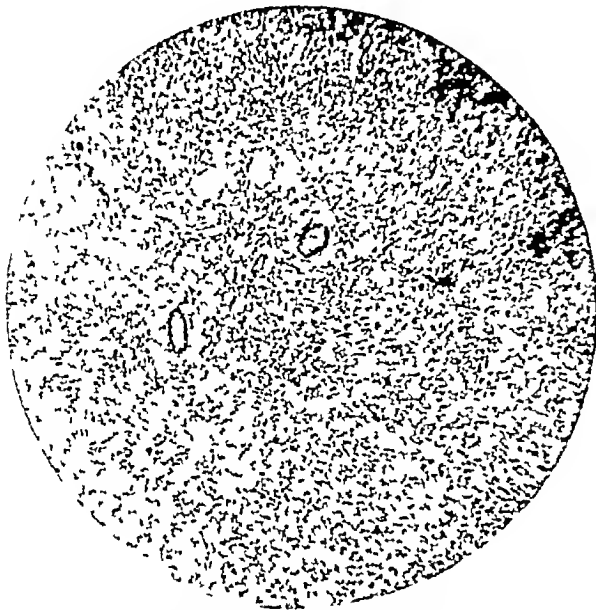


FIGURE 8 *Carcinosarcoma (Case 13), Demonstrating Another Area from the Tumor Shown in Figure 7*

of the radium on the size of the growth is not recorded. The patient survived eleven months.

In Case 15 x-ray therapy (2412 r) was given through each of two portals postoperatively because at operation small seedings of tumor were noted on the small bowel and in the liver. The patient died in three and a half months without showing improvement at any time. The patient in Case 13, described in greater detail below, received little or no benefit from x-ray therapy for recurrent tumor.

From the above cases, and the 2 patients with leiomyosarcomas previously mentioned as having received radiation therapy, one concludes that palliative roentgenotherapy is of little if any value unless it is to give the patient hope. The findings in Case 14 suggest that, as in carcinoma of the endometrium, preoperative radium destroys tumor projecting into the uterine cavity and thus prevents its dissemination in the operative field when the uterus is removed.

The following cases are of great interest in that the patients were treated with radium six and nine years prior to discovery of the sarcomas. Although the possibility seems remote, an etiologic role of the radium must be considered. These cases are

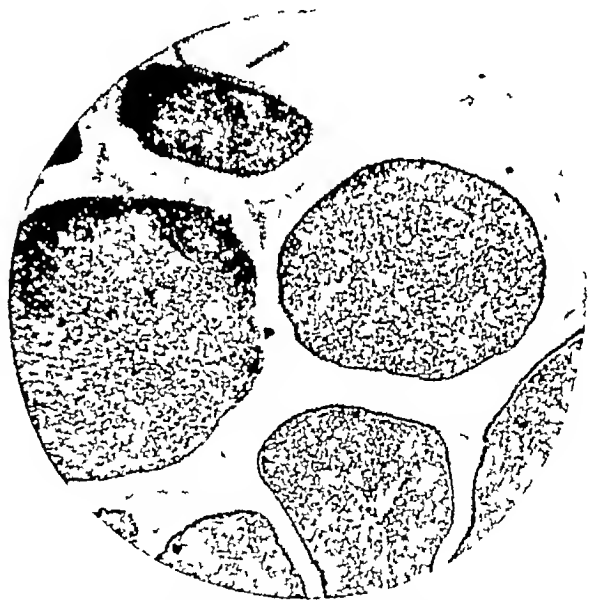


FIGURE 9 *Sarcoma Botroides (Case 18), Showing the Peripheral Grape-Like Projection*

On May 21 a morcellation of what appeared to be a submucous fibroid presenting at the cervical os was done. Microscopically this turned out to be a sarcoma, which was called stromal cell. On June 4 a Wertheim hysterectomy was performed, and histologic examination revealed a few areas of epithelium (Fig 7 and 8), the diagnosis was carcinosarcoma.

The patient had a local recurrence of tumor in 18 months and died of the carcinosarcoma 38 months after hysterectomy. X-ray therapy given on two occasions did not seem to influence the slow progression of the recurrent tumor.

The following case is also presented in some detail. Unfortunately, only four months have elapsed since operation and the ultimate outcome is uncertain, but the tumor is interesting enough histologically to warrant some discussion.

CASE 18. J S, a 514-month-old infant, entered the hospital on January 15, 1947. She had been healthy from birth until 5 hours before admission, when she had a sudden onset of profuse vaginal bleeding. She appeared normal except for a firm globular mass rising out of the pelvis to the umbilicus. Bleeding continued, and on the 2nd day a laparotomy was performed as a life-saving measure. The uterus was found enlarged and was opened in the midline, exposing a soft, grape-like mass of tissue measuring 5 by 5 by 0.8 cm. This was evacuated, leaving a smooth-lined endometrial cavity. A pathological diagnosis of sarcoma botroides was made and further surgery was advised but refused by the parents in view of the poor prognosis regardless of treatment. The child was alive without evidence of recurrence 4 months post-operatively.\*

Sarcoma botroides usually arises in the portio of the cervix and extends down into the vagina. In Case 18 the tumor filled the corpus uteri. Inasmuch as the exact origin of the tumor was not visualized at operation, but the entire endometrial cavity was smooth, it is assumed that the tumor arose from the cervix and for some reason protruded up instead of down.

Striated muscle fibers in a tumor of this type are considered pathognomonic of sarcoma botroides. They cannot be shown in this case but other characteristics are quite in accord with this diagnosis. Several areas within the tumor are of great interest histologically, since they help clarify the histogenesis of this tumor and possibly of others. There are large areas of a loose myxomatous tissue. The grape-like projections consist of closely packed cells with uniform, round, ovoid nuclei and little cytoplasm surrounded by cuboidal epithelium (Fig 9). Most noteworthy are areas of tubules lined by columnar or pseudostratified epithelium (Fig 10). These tubules closely resemble those of a fetal nephros, and structures simulating glomeruli can be picked out.

Wilms,\* in 1899, advanced the theory that mixed sarcomas of the uterus originate in displaced myotome and sclerotome elements carried down by the wolffian ducts. Glass and Goldsmith<sup>10</sup> concur in this opinion, and Case 18 seems to offer further support.

### SUMMARY

A brief account of the characteristics of various types of uterine sarcomas is given.

Eighteen cases treated at the Rhode Island Hospital since 1929 are recorded, and their classification is discussed.

A generally poor prognosis is recorded. The importance of few mitotic figures as evidence of a favorable outlook in leiomyosarcoma is supported.

There was a lack of evidence that leiomyosarcomas arise from pre-existing leiomyomas. In only 1 case were the two types of tumors found to coexist.

\*Information received after the preparation of this paper indicated that the patient developed a suprapubic mass ten months post-operatively and passed tumor tissue by vagina two months later.

Eight patients received radiation therapy of some sort. X-ray treatment seems to be of little palliative value. One case appeared to be favorably influenced by preoperative radium applied to the uterus, as evidenced by necrosis in the subsequent pathological specimen.

Four cases reported in detail comprised a leiomyosarcoma with late metastasis to the humerus, a

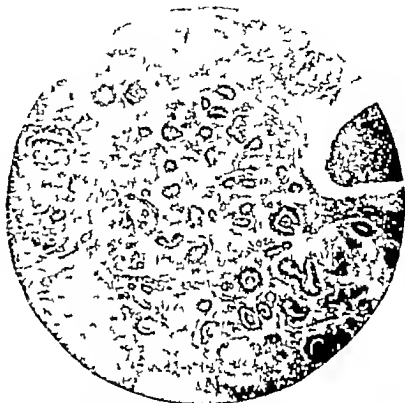


FIGURE 10. Sarcoma Botroides (Case 18) Showing an Area Resembling Wilms' Tumor of the Kidney

mixed mesodermal sarcoma and a carcinosarcoma occurring after radium treatment of menopausal bleeding, and a sarcoma botroides in an infant.

I am indebted to Dr. George W. Waterman for his advice in the preparation of this paper and to Dr. B. Earl Clarke for guidance in the study of the pathological material.

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## THE PONDVILLE STATE CANCER HOSPITAL, 1927-1947

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SHORTLY after World War I, a movement was instigated in Massachusetts to provide care and treatment for patients with cancer. For many years various persons prominent in both public and private life became interested in the problem. The health officials believed that this was outside the realm of Public Health, but the public demands for some kind of a state-wide cancer-control program were so great that the Legislature in 1926 passed an act "to promote the prevention and cure of cancer and the extension of resources for its care and treatment." The bill originally called for the expenditure of \$1,500,000 for the construction of a modern hospital to be located in or around Boston, but for some reason, no money was appropriated when the bill was passed. At that time there existed in the town of Norfolk, twenty-two miles south of Boston, on Route 1-A, a group of vacant buildings known as the Norfolk State Hospital, — formerly used by the Massachusetts Department of Mental Health for the rehabilitation of narcotic and alcoholic habitués, — which could be renovated and utilized for the proposed state cancer hospital. Therefore, the Legislature amended the original bill and appropriated \$100,000 to renovate this group of buildings. Thus, Massachusetts became the first state in the country to appropriate funds for the construction and maintenance of a hospital to be used solely for the diagnosis and treatment of cancer.

The Massachusetts Department of Public Health, under mandate of the Legislature, opened the Pondville State Cancer Hospital on June 21, 1927. At first there was some question whether its 90 beds could be filled, but within a year the hospital was filled to capacity and had a large waiting list. Because of the demands, an addition for 25 beds was constructed, which only made a dent in the waiting list. The medical staff consisted of a medical superintendent and 4 residents, all graduates of surgical or rotating services of general hospitals. The nursing, in charge of a superintendent of nurses, was carried on by 19 graduate and 31 attendant nurses. A training school for attendant nurses was conducted with a course of one year. The visiting staff was made up of 17 men, all working on the cancer problem in other institutions in Boston or elsewhere, but none of them limiting their work to cancer.

The Pondville Hospital today has a capacity of 139 beds. These beds are in pavilions, each hav-

ing numerous single rooms and several 2-bed and 4-bed wards. These pavilions have large airy porches, comfortable rooms and the necessary diet kitchens — in fact, all that helps to make a person who is ill and away from home and friends more comfortable. There are four operating rooms with equipment of the most modern type, two deep-x-ray-therapy machines, which are now considered essential in the treatment of cancer, a gram of that very expensive but very necessary element, radium, numerous radium needles encased in platinum and an electrosurgical unit. There are also chemical, bacteriologic and pathological laboratories, all essential to a modern hospital, and a medical library to keep the members of the staff informed of world trends in the progress toward the solution of cancer. Practically from its opening, this hospital has been approved by the American Medical Association and the American College of Surgeons, an indication that it meets in all particulars the exacting requirements of an up-to-date hospital.

The visiting staff, composed of 27 men representing all the medical and surgical specialties, receive salaries from the Commonwealth. Many of these men devote two and a half days a week to the work of the hospital, and others half a day, still others are called as the occasion arises. These men are all working on cancer in other institutions and are deeply interested in its problems. The resident staff consists of the medical superintendent, who lives on the grounds, and 10 resident physicians, all men who have graduated from surgical and rotating services of general hospitals.

One of the important services of this hospital is the general clinic for new and ambulatory patients and for follow-up work. Here consultations are held by groups of visiting surgeons, with a radiologist, an internist, a dentist and a laboratory technician present to make the necessary examinations. No matter how advanced the case or how obvious the condition, thorough examinations by x-ray study and other special procedures are made. Special clinics are held on other days by appointment for follow-up work. As in any good state cancer-control program, it is necessary to have a central focus of activity, so does the Pondville Hospital act as a nucleus for seventeen state-aided cancer clinics situated in seventeen cities and towns. Cases difficult to diagnose are referred from the clinics to Pondville.

The Social Service Department at Pondville is also an important factor in its work because in cancer, as in every disease, the early diagnosis and

\*Superintendent, Pondville State Cancer Hospital

treatment depend not only upon the doctor's examinations and recommendations for treatment but also upon the patient's carrying out this advice. This, in turn, is dependent upon the patient's environmental conditions and economic resources, and it is here that the medical Social Service Department is of great value. The Social Service Department at the Pondville Hospital serves both the outpatients and the house patients. Thus, the Social Service Department, whenever possible, interviews the patient before he enters the hospital, assists him whenever and however possible while he is in the hospital and performs a valuable service in the follow-up work after he has been discharged. Uniform records are kept, and statistical studies are frequently made.

A volunteer social-service committee, comprising a group of women from neighboring towns, a local minister and a parish priest, provides many little luxuries for the comfort of both patients and employees. Recently, funds have been given to this committee by the Massachusetts Division, Incorporated, of the American Cancer Society to assist in the care and treatment of patients after they are discharged.

In 1928 the Legislature enacted a law regarding admissions and charges at Pondville. This act limits admission to residents of Massachusetts who have lived in the Commonwealth for at least twenty-four out of the last thirty-six months prior to the date of application and requires the written application of a registered physician or dentist. Persons who are able to pay their own bills pay \$10.50 a week. If a person is unable to pay, the city or town in which he has a legal residence is assessed at the rate of \$17.50 a week. Every patient, whenever possible, regardless of his financial status, is given a single room and as much individual attention as his condition requires. There is no classification of a ward or a private patient. The few wards of two and four beds are for patients able to be up and about. The Pondville personnel, from the lowest to the highest position, co-operate in giving the patient every service and in making him comfortable mentally and physically.

Daily visits are made by the priests and ministers from neighboring parishes, and current literature is distributed twice weekly for those requiring reading material. For those who enjoy the radio, bedside earphone attachments are available.

When a patient is discharged from the hospital, he is referred back to his family doctor or the clinic doctor who referred him to the institution. A letter is sent to this person giving the diagnosis, treatment and prognosis, with the advice that there be a continuous follow-up, both under his supervision and in the outpatient clinic of the Pondville Hospital. In this way harmony and co-operation are maintained between the hospital and the private physician.

TABLE 1 Total Cases of Cancer from 1927 through 1946

DIAGNOSIS	MALE PATIENTS	FEMALE PATIENTS
<b>Carcinoma</b>		
Buccal cavity and pharynx	1893	166
Digestive system and peritoneum	1,566	661
Respiratory system	481	68
Female genital organ	—	2,017
Breast	18	1,685
Female genital organs	—	17
Male genital organs	528	—
Urinary organ	315	99
Skin	2,175	1,059
Other unspecified sites	244	173
Aureal gland	3	1
Bladder	19	1
Bone (primary source unknown)	41	10
Brain	9	5
Heart	—	1
Rat	1	—
Thyroid	23	26
Uterus	1	—
Primary source unknown	75	49
Questionable	72	80
<b>Other malignant tumors</b>		
Chondroma	1	—
Endothelioma	7	7
Angioid endothelioma	2	—
Endothelioma	1	3
Hemangioendothelioma	4	3
Lymphangioendothelioma	—	1
<b>Epithelioma</b>		
Cheiloepithelioma	—	2
<b>Leukemia</b>	52	18
Leukosarcoma	1	—
Lymphatic leuk. mia	11	11
Myelogenous leukemia	16	6
Osteomyeloma	4	1
<b>Lymphoma</b>	237	137
Giant follicle	9	1
Hodgkin's lymphoma	120	66
Lymphoma unspecified	43	29
Lymphocytoma	—	—
Lymphosarcoma	41	34
Lymphosarcoma (reticulum-cell type)	5	4
Lymphosarcoma	3	2
Thymoma	—	1
Polymorphous-cell sarcoma	—	1
<b>Melanoma</b>	75	70
Mixed tumor	3	3
Plasmacytoma	85	93
<b>Sarcoma</b>		
Adenofibrosarcoma	—	11
Adenomyosarcoma	—	3
Angiofibrosarcoma	1	1
Angiosarcoma	3	1
Fibrosarcoma	38	19
Fibrosarcoma neurogenic	9	9
Leiomyosarcoma	6	25
Lipomyosarcoma	2	3
Liposarcoma	1	—
Mixed-cell sarcoma	1	1
Myofibrosarcoma	2	1
Myxofibrosarcoma	1	1
Myxosarcoma	2	3
Rhabdomyosarcoma	2	1
Sarcoma	12	12
Sarcoma Kaposi type	4	—
Spindle-type sarcoma	—	—
Xanthosarcoma	1	—
<b>Teratoma</b>	8	—
Malignant tumor type unknown	35	24
Questionable malignant tumor	19	10
<b>Bone tumor</b>	76	44
Osteogenic	42	21
Chondroma series	8	2
Giant-cell tumors malignant	1	—
Ewing sarcoma	11	8
Myeloma series	1	1
Malignant bone tumor type unknown	2	1
Questionable malignant bone tumor	2	4
Chordoma (embryonic remnant)	—	2
Tumors of dental origin (adamantinoma)	—	—
<b>Tumor of nervous system</b>	11	12
Astrocytoma	—	2
Glioblastoma	—	—
Glioma	—	—
Medulloblastoma	1	1
Melanoma	—	1
Neuroma	—	2
Neuroblastoma	3	—
Neuroepithelioma	1	1
Retinoblastoma	1	1
Type unknown	1	1
Questionable	2	1



The purpose of the Pondville State Cancer Hospital is threefold to provide adequate care for patients unable to be accommodated elsewhere, to stimulate more adequate diagnostic and therapeutic service for cancer in clinics, and to train physicians, surgeons and nurses in the diagnosis, treatment and general care of patients with malignant lesions. During the past twenty years, under the supervision of four successive commissioners of public health and three superintendents, the Pondville Hospital has hospitalized 21,277 patients, of whom 14,015 were new cases and 7,262 were readmissions. During the early days, upon admission the majority of patients were in the advanced stages of the disease, whereas in the last decade most of the patients were early cases and represented a fair cross-section of cancer as it has occurred in Massachusetts. Major operations were performed in 18,325 cases. The total deaths num-

bered 3,453, and in 57 per cent of the cases permission for autopsy was granted. In the outpatient clinics 101,943 patients were examined, of whom 19,153 were new cases and 82,790 patients were follow-up cases.

have settled in Massachusetts, and the others have settled in twenty-two states and three different countries. Many of these men have returned to their native states to practice and, so far as can be learned, are doing their share of the cancer work in their respective localities. This is particularly true of the 56 physicians who have settled in Massachusetts. Four surgeons have died, and the status of 11 other men is unknown.

Table 2 shows the location by country and state. Fifteen years ago, the late Dr. George H. Bigelow, then commissioner of public health, and Dr. Her-

TABLE 2 Subsequent Location of Physicians and Surgeons Trained at Pondville State Cancer Hospital

LOCATION	No. of MEN
Canada	2
China	1
Mexico	1
United States	120
California	1
Colorado	1
Connecticut	2
Delaware	1
Georgia	1
Illinois	3
Iowa	1
Kentucky	1
Louisiana	1
Maryland	1
Massachusetts	56
Mississippi	1
Missouri	1
Montana	1
New Hampshire	3
New Jersey	2
New York	13
Pennsylvania	7
Rhode Island	3
Texas	1
Vermont	2
Washington	2
Unknown	11

bered 3,453, and in 57 per cent of the cases permission for autopsy was granted. In the outpatient clinics 101,943 patients were examined, of whom 19,153 were new cases and 82,790 patients were follow-up cases.

Table I includes all cases that were diagnosed as malignant, and since the members of the visiting and resident staffs have reported the results of the treatment given these patients in the current medical and surgical journals during this twenty-year period, no attempt is made to analyze these figures.

The Pondville Hospital, to date, has not only completed the first two of the original purposes for which it was established but also trained 124 physicians and surgeons in the specialized treatment of malignant tumors. Of these, 21 men received special training in pathology. Many of the men

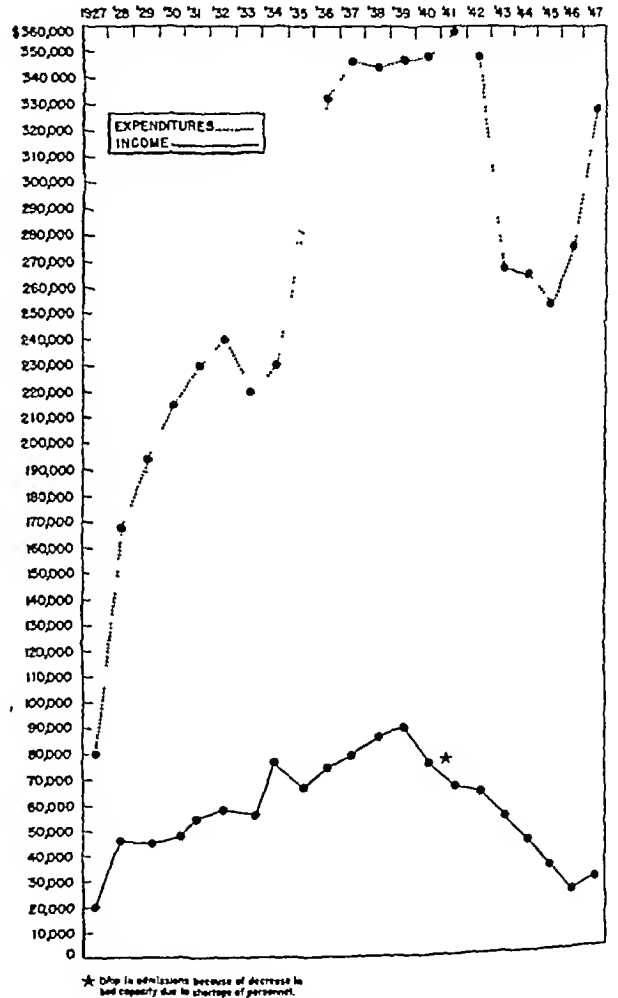


FIGURE 1 Expenditures vs Income Over Twenty-Year Period

bert L. Lombard, director of the Division of Cancer and Other Chronic Diseases in their book entitled *Cancer and Other Chronic Diseases in Massachusetts* wrote "to give what would seem to be the most intelligent service in the field of recognition, cure, and alleviation, costs hundreds of thousands to millions of dollars." Truer words were never written, for the service rendered by Pondville during the last twenty years has cost the Commonwealth over \$5,500,000, and

this figure does not include the cost of additional building construction during this period. To be sure, more than \$1,250,000 was collected from patients and the public-welfare boards in the various cities and towns as prescribed by the legislative acts of 1927, but the collections never balanced the expenditures (Fig 1).

Figure 2 illustrates the fact that during the last six years the strictly indigent patient has been in the minority, for the greatest income has been collected from private sources—that is, from the

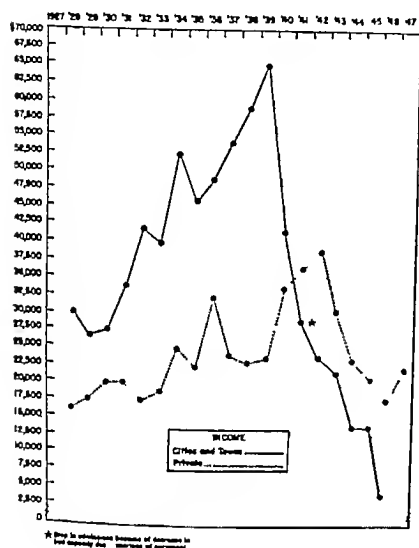


FIGURE 2. Patient Income vs Income from Cities and Towns over Twenty-Year Period.

patient. However, the charge to the private patient represents only a fraction of the cost of treatment, and the greater part of the patients admitted are in fact medically indigent.

The ravages of World War II not only produced an increase of hospital expenditures but also caused a great upheaval in our hospital personnel. Like many other institutions, Pondville has been forced to decrease its active bed capacity to 40 patients because of the lack of graduate and attendant nurses. In spite of these factors, the turnover of patients in the hospital and in the outpatient clinics reached approximately prewar figures (Fig 3). This was due to the careful selection and screening

through the general clinic of the cases admitted to the hospital.

Table 3 explains the preceding charts and demonstrates the hospital activities on a yearly basis,

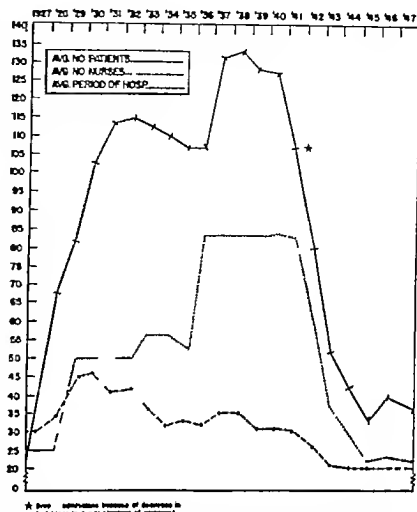


FIGURE 3. Proportion of Active Beds vs Available Nurses and Decrease in Average Period of Hospitalization over Twenty Year Period.

with special reference to the average number of house patients, the average period of hospitaliza-

TABLE 3. Hospital Activities from 1927 to 1947

YEAR	AVERAGE NO OF PATIENTS	AVERAGE PERIOD OF HOSPITALIZA- TION Days	AVERAGE NO OF EMPLOYEES	TOTAL CLINIC VISITS
1927	31.2	30.30	50.0	133
1928	67.6	34.48	59.0	1,343
1929	82.18	46.83	75.0	1,502
1930	100.3	47.75	95.0	2,185
1931	113.5	43.99	110.0	2,805
1932	114.1	44.04	125.0	3,501
1933	102.0	37.3	130.0	4,429
1934	110.0	35.8	120.0	4,620
1935	107.0	34.0	144.0	4,638
1936	107.0	35.0	144.0	4,991
1937	131.0	35.4	191.0	5,332
1938	132.0	35.0	195.0	5,769
1939	128.0	31.3	196.0	6,908
1940	127.5	31.9	196.0	7,678
1941	106.0	30.3	196.0	7,654
1942	80.8	27.9	160.8	6,345
1943	51.6	22.4	112.0	6,084
1944	41.8	21.8	103.0	6,815
1945	34.1	20.5	89.51	6,205
1946	40.3	20.7	92.64	7,023
1947	40.75	19.01	110.8	8,055

tion, the average number of available employees and the outpatient clinic visits

The peak of the patient and employee load was reached in 1938, and although the patient load fluctuated because of the type of cases admitted, the employee load remained constant until the year 1942. At this point the effects of World War II began to be felt, especially the lack of nursing personnel, and, consequently, only such patients were admitted as could be efficiently and adequately handled. It will be noticed that the average period of hospitalization reached a peak in 1930 and dropped annually to the low level of nineteen days, whereas the total outpatient visits steadily increased annually up to 8085. In passing, it is of interest that the daily cost to the Commonwealth for these services in the early days was five dollars per patient day. Twenty years later, and particularly during the post-war period, this figure has been multiplied many times.

The people of the nation, particularly the citizens of Massachusetts, laymen as well as physicians, have become more conscious of cancer during the

last five years, and public opinion, having been aroused, has resulted in not only a greater need for beds for the cancer patient but also a demand for more intensive cancer investigation. In 1947 the Legislature, to meet the local needs, approved the expenditure of \$600,000 for the construction of a power plant and a 100-bed nurses' home and recreation building. The Massachusetts Department of Public Health has recommended to the Legislature the expenditure of over \$2,000,000 for additional buildings during the next five years to keep Pondville abreast of recent developments in the prevention and treatment of cancer.

Massachusetts citizens should be proud of the progress that the Pondville State Cancer Hospital has made in the battle to eliminate one of the greatest killers. For twenty years it has been the leader in this fight, and today stands as a tribute to those who worked so earnestly to make possible modern hospitalization for all its citizens who are in need of its services.

## UNUSUAL REACTION TO PENICILLIN IN OIL AND WAX

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AS new forms and combinations of penicillin have been developed, the reported incidence of hypersensitivity has also increased. Keefer<sup>1</sup> states that the incidence of hypersensitivity following the use of amorphous penicillin in aqueous solution has varied between 2 and 5 per cent. Although there is a belief that hypersensitive reactions are somewhat greater when penicillin in peanut oil and beeswax is used, conclusive evidence is not yet available.<sup>2</sup> Beeswax itself has been regarded as nonantigenic,<sup>3</sup> but some authorities think that certain persons may become sensitized to it.<sup>1</sup> Extensive studies have failed to show that pollen extracts are carried over in beeswax.<sup>2</sup> Some evidence has accumulated that the sensitization is to the penicillin itself and not to the oil and wax, for patients who receive penicillin in aqueous solution, after being sensitized by use of penicillin in oil and wax, have typical allergic reactions.

Romansky,<sup>4</sup> in a series of approximately 4000 cases treated with penicillin in oil and beeswax, reported allergic reactions in about 5 per cent. The reactions varied from slight urticaria to edema of the angioneurotic type. These reactions reached a maximum within four days of appearance. If the injection was given subcutaneously a local reaction occurred more frequently. Heat to the area

aggravated the symptoms, whereas cold and the antihistaminic drugs gave relief. Thus, it appears that these reactions were truly allergic ones and not due to tissue injury. The Arthus phenomenon—local edema and necrosis following subcutaneous injection of the specific antigen—has not been reported.

Lederman<sup>5</sup> reported a case of severe local reaction after ten injections of penicillin in oil and beeswax, a total of 3,000,000 units having been given prior to the reaction. Another manufacturer's product did not give a reaction when the injections were resumed. Switzer<sup>6</sup> reported an acute local reaction one week after a single intramuscular injection of 300,000 units in a patient who had previously taken penicillin lozenges. In our practice 2 cases have exhibited urticaria and pruritus seven to nine days after a single injection of penicillin in oil and beeswax, no history of previous penicillin usage could be established. The third case is so unusual that it is reported in detail.

### CASE REPORT

A 29-year-old married man was first seen on November 18 complaining of a furuncle of the left nostril, which had first been noticed on the preceding morning and had rapidly increased in size by the late afternoon. The only treatment had been hot compresses.

The past history was essentially irrelevant except for hypersensitivity to ragweed, which was controlled by pre-seasonal and co-seasonal desensitization treatment as well as antihistaminic drugs.

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Physical examination disclosed a furuncle the size of a small lima bean in the left nostril; the surrounding area was inflamed, firm and very tender. The nostril was almost completely occluded by the furuncle.

The temperature was 99.2 F.

At 9 a.m. the patient was given 300,000 units of penicillin in oil and beeswax (Romansky) intramuscularly in the anterior aspect of the midportion of the left thigh. Soon afterward some pain was present at the injection site. At 3 p.m. the area from there down to the left knee was tender in the touch and active motion was painful. Three hours later the area was so sensitive that the weight of a blanket caused pain and motion was not possible. The temperature was 99.6°F., and headache and malaise were present. No signs of injury or tissue damage were visible, nor was there any change in the size or contour of the involved area. Treatment consisted of bed rest with ice packs and salicylates.

On November 19 the pain had diminished slightly and some active motion was possible. Serous exudate was present at the left knee joint; the entire area otherwise appeared normal. Weight bearing was painful. Since the furuncle was still inflamed and firm the patient was given 100,000 units of crystalline sodium penicillin G in aqueous solution into the right buttock. No immediate hypersensitive reaction followed. Another similar injection was given on the following day without reaction. In the next few days the symptoms gradually disappeared except that the left knee hurt on walking. The furuncle was healed on November 23. Treatment for the left knee-joint exudate was ice packs since heat aggravated the symptoms.

On the 9th day after the initial injection the entire area suddenly developed a pruritic urticaria, and the left knee joint exudate reappeared. Pyriminexamine in 50-mg doses controlled the pruritus. By November 28 the left thigh was 3 cm. larger than the right, and the skin on the anterior aspect had a thick, doughy texture. Very little pain was present, and normal activity was possible. On December 1 the left ankle was also swollen, being 2 cm. larger than the right. The left thigh was enlarged 2.5 cm. and the calf 1 cm. All edema was gone on December 5, and the only residuum was a noninflammatory, red area at the site of the injection on the right buttock.

### DISCUSSION

Since the patient denied having previously received penicillin in any form, he was questioned regarding his allergic history in an effort to establish an allergic basis for the early acute reaction. He stated that at least once each summer,

during the period of ragweed allergy, the left knee joint became edematous and remained so for several days. Thus, one etiologic source in this case may have been the presence of ragweed pollen in the beeswax, although such pollen has not been found in beeswax in previous studies.<sup>2</sup> A second possible cause may have been an early serum-sickness type of reaction to the penicillin. Kendig and Toone<sup>7</sup> reported 3 cases in which a serum type of reaction developed five to seven days after oral administration of penicillin had been discontinued. These were delayed reactions characterized by fever, sensitivity to touch and swelling of the wrist and ankle joints. There are no reports in the literature on reactions to penicillin as early as that in the case described above.

### SUMMARY

A case of both acute early and delayed reactions to penicillin in beeswax and peanut oil is presented. Two possible etiologies are suggested.

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## MEDICAL PROGRESS

### PILONIDAL CYST AND SINUS

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THE ideal of all surgical treatment is to effect a cure, and in pilonidal cyst and sinus the basic aim is to prevent recurrence, lessen the period of disability and obtain a good mechanical result. The various methods presented in the literature by skillful surgeons attest to the fact that the search is not easy, although a number of men seem to have found the key to the problem.

This paper, therefore, presents a review of the literature, with a follow-up of constructive criticism, and the presentation of my technic, which is considered a rational approach to the problem and has resulted in 100 per cent cures.

Naturally, one would be less than human if he did not think his method superior, especially if excellent or relatively excellent results were usually obtained. One may disagree with the other man's procedure, or hold it in light regard. But it is best to remember that a certain method may work well in the hands of one surgeon and yet prove disastrous when another attempts it with seemingly the exact technic — the reward going to the former, who may have used certain imponderable niceties and nuances in the successful performance of his task.

Those who find a certain method newfangled or bizarre should keep in mind the following thought well expressed by Cutler and Zollinger<sup>1</sup>:

Every change in the practice of surgery has aroused violent opposition. There was a battle between Lister and his opponents — the introduction of the x-ray elicited bitter criticism on the part of the conservative practitioners of that day. More recently the introduction of the electric scalpel and of the many forms of electricity for cutting and for coagulation has brought bitter opposition and slow acceptance.

The term pilonidal cyst or sinus, from "pilus" (hair) and "nidus" (nest), comprises an abnormal opening in the midline skin superior to the anus in the gluteal cleft over the sacrococcygeal region. The defect is lined with epithelium, and may contain cellular debris, hair and sebaceous material. Sharpe<sup>2</sup> has written the following description:

The tract is lined by poorly developed epithelium, and before the stage of infection, there may be some excretion of the products of skin metabolism through the orifice. If the orifice becomes blocked by accumulated debris or following an injury, the retained secretion may form a cyst or more commonly become infected and form an abscess. If the abscess ruptures without benefit of the surgeon, as is often the case, a fistulous opening is formed,

if it closes, a secondary abscess may form later, and so the process may be repeated several times before the patient seeks surgical relief.

According to Granet and Ferguson,<sup>3</sup> the term "pilonidal" is not necessarily correct, since most cysts do not contain hair. The authors state that the hair is extraneous and has its origin in the hair follicles of the skin of the natal fold adjacent to the sinus or dimple. Through the trauma of friction between the skin surfaces, some protruding hairs are broken off and retained in the sinus, through years of accumulation and by constant moulding from external pressure, they eventually become compressed and kneaded into hair nests.

#### TYPE

Gage's<sup>4-6</sup> classification is simple and clear: sacrococcygeal dimple and sacrococcygeal dimple and sinus, true pilonidal sinus confined to the subcutaneous tissue, true pilonidal cyst extending to the sacral canal, and true pilonidal cyst continuous with the subarachnoid space and canal of the spinal cord.

#### ETIOLOGY

Several interesting theories regarding etiology may help to explain the pathology and act as a guide toward rational treatment of this condition. Mallory<sup>7</sup> declares that the causation embraces the principle of captured ectodermal cells in the subcutaneous tissues and soft parts, the condition is due to captured ectodermal cells occurring at any stage during the development of the medullary canal or to faulty obliteration of the canal itself, or to a combination of both factors.

Weeder's<sup>8</sup> conclusion is that the included ectodermal cells may be limited to the soft parts, extending to and caught in the dorsal arches of the vertebrae, or may be continuous with or captured in the medullary canal, or the latter may leave unobliterated remnants either with or without spinal bifida occulta anywhere below the second sacral segment. They may extend to the skin through a sinus or remain as a cyst. It is interesting that Rogers and Dwight,<sup>9</sup> in a series of 400 cases, have found none to have communication with the neural canal, attesting to the rarity of this complication.

Fox,<sup>10</sup> in a detailed study, concludes that the pilonidal cyst is a congenital lesion due to a process of normal ectodermal invagination in the embryo,

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which usually disappears but in these cases has persisted in adult life. It commonly contains fine, silky hair and mucoid or gelatinous material, it is almost always infected, and its walls consist of several layers of epithelial cells with glands and hair follicles. Derived from the budding or growth centers in the basal layer of the ectoderm that gives rise to hair follicles and glands, it consists of cells that form only hair and glandular appendages. For this reason, according to Fox, one never sees teratoma, neurogenic growths or heterologous tumors in pilonidal sinus.

Gage<sup>4</sup> is the chief proponent of the neurogenic theory; he believes that the condition is due to persistence of the neurenteric or neural canal. Normally, in the caudal end of the embryo, the portion of the neural canal that is formed by union of the neural folds and lies between the skin and coccygeal vertebrae is obliterated by cohesion of its walls, failure to do so forms a cavity, which may be connected with the skin by one or more sinuses. The lining of the cystic cavity retains the faculty of producing the primitive skin appendages: the hair follicle or shaft, and a rudimentary type of nervous tissue if a connection with the spinal canal remains. Gage regards this as the true origin of pilonidal sinus and believes that the sacral dimple is the result of an anterior pull on the overlying skin by the caudal ligament as the coccyx grows downward and curves anteriorly.

#### INCIDENCE AND DISTRIBUTION

Sharpe<sup>5</sup> states that 20 to 25 per cent of all infants examined at birth and about 4 per cent of a larger group of adults present either a distinct dimple or depression of the skin at the sacrococcygeal region. These always remain symptomless. Actual sinus orifices are seen less frequently, the exact incidence being unknown. The average age at which annoyance first occurs is nineteen years, with the incidence two or three times as great in males. McKirdie<sup>6</sup> states the incidence among Negroes as compared to that among whites to be 1.2150, or negligible, with no reports in the yellow, brown or red races.

#### DIAGNOSIS

The sinus consists of small midline openings over the sacrococcygeal region, with an occasional tuft of hair protruding from the opening. When the sinus is infected, pus may exude from the openings. The area may be red, swollen and indurated, showing signs of a superimposed abscess.

#### TREATMENT

##### Röntgen-ray Therapy

Smith<sup>12</sup> uses roentgen-ray irradiation to inhibit hair growth from interfering with healing.

control infection. He presented 6 cases in which the final results were inconclusive.

Turell<sup>13</sup> reported a case in which 675 r was applied to the perineum and sacrococcygeal area over a period of two months, the sinus closed shortly before cessation of the treatment, and remained closed for five months, thereafter the patient disappeared, making it impossible to observe him further for ultimate results. In another case, 650 r was used over a six-week period, and the sinus has remained closed to date (two years).

Sher<sup>14</sup> obtained gratifying results in cases with a small sinus and small discharge and in cases with a short clinical history.

##### Sclerosing Solutions

Cutler and Zollinger,<sup>1</sup> observing the successful use of fixatives by the neurologists for gliomatous cysts, became interested in such a method for pilonidal cysts and sinuses. In the 3 cases presented, the roof of the sinus was incised, the edges being protected with zinc oxide, and the cavity filled with 1 to 5 cc of modified Carnoy's solution (3 cc of absolute alcohol, 3 cc of chloroform, 1 cc of glacial acetic acid and 1 gm of ferri chloride). This was allowed to remain for five to ten minutes and then sponged out, and the destroyed tissue curetted away. This procedure was repeated every two weeks, at times daily, gauze was inserted after exposure to the solution.

Biegeleisen<sup>15</sup> presents 3 cases with a one-year cure. The sinuses are probed, and a modified Carnoy's solution is injected, a dull-tipped needle being used. Two weeks later the sinuses are curetted (2 per cent nupercaine being employed) with a fine curette or a needle having a long bevel, bent to form a slight hook, then fuming nitric acid is applied on an ordinary metal applicator deeply within the sinuses. Two weeks later this procedure is repeated. One month later it is difficult to enter the tracts, and still a month later the tracts are completely closed.

Mathesheimer<sup>16</sup> uses ethyl laminobenzoate (twenty-five parts) and phenmethylol (seventy-five parts). The abscess or sinus is opened under skin infiltration. The tract is opened on a probe or grooved director at different stages, so as not to cause too large a wound. The wound is swabbed out, and plain gauze, saturated with the solution, is inserted, this procedure is repeated until healing has reached the surface.

Knowlton<sup>17</sup> uses 10 per cent sodium morrhuate, injecting 2 cc, and repeats the procedure in three or four days. Of 4 cases presented, 4 were completely cured.

Heyd<sup>18</sup> excises an ellipsis of skin carrying all the "dimples" and packing the cavity with modified Carnoy's solution. The gauze is left in for forty-eight hours, and the patient is treated in a similar manner every 5 days, with plain gauze in the interim.

five cases were presented, all successful Heyd claims that this method makes the walls of the wound rigid and firm, and that the cavity heals readily and rapidly

Shafiroff and Doubilet<sup>19</sup> used a mixture of penicillin and sodium morrhuate (5 cc of 5 per cent sodium morrhuate to 100,000 units of dry penicillin), 1 cc was injected directly into the cyst or sinus tract the first time, and as sclerosing progressed, small amounts were injected daily and then every other day Twenty-seven cases were presented, with a minimum of four to a maximum of forty-six injections After two or three injections the drainage from the orifices subsided rapidly A follow-up study over a three-month period showed recurrences in 3 cases

### Cautery Excision

Rogers is a leading exponent of the use of the cautery knife In a series of 181 ambulatory cases this technic was employed by Rogers and Hall<sup>20</sup> The method, in brief, consisted in repeated excision with cautery of the diseased tissue The sinus was first divided longitudinally down to the sacrococcygeal fascia, and then removed in halves by slight undercutting of the skin edges Postoperatively, further fractional removals were effected for portions overlooked originally The loss of time from work was less than two weeks At the time of publication, Rogers and Hall believed that there was room for improvement In an article written in 1938 Rogers and Dwight,<sup>9</sup> concluded that it was not necessary to remove or expose the sacral fascia At that time, in a large series of cases of undisclosed number, 90 per cent were cured in less than fourteen weeks, 80 per cent in less than twelve weeks, and 64 per cent in less than ten weeks, with a minimum of five weeks In a 1940 publication, Rogers<sup>21</sup> recommended conservative cautery excision under a local anesthetic in the outpatient department. The sinus tract and hair nest were dissected out through the midline skin incision with the small cautery blade, the resultant narrow wound was packed with gauze The shortest healing time was four weeks, with an average of nine weeks One hundred and fifty operations were done between 1935 and 1937, 14 in the hospital and 136 in the outpatient department, and 97 per cent were cured by conservative excision, remaining cured for one to four years On this basis, Rogers is against large block excision

Hipsley<sup>22</sup> excises the sinus by cautery and then makes an incision 7.6 cm lateral to the wound above the ischial tuberosity in the line of the fibers of the gluteus maximus muscle, a flap of muscle sufficiently thick to fill the cavity and to reach the opposite wall through the tunnel without tension is freed, the wound being closed loosely

### Marsupialization

Dorland<sup>23</sup> defines marsupialization as an operation for hydatid or other cyst in which the tumor is opened, its contents emptied, and its edges stretched to the edges of the external incision The interior of the sac so formed suppurates and closes by granulation Buie,<sup>24</sup> one of the chief exponents of this method, argues that the deeper half of the lining of the cyst cavity, since it was originally intended to form skin, can be used to advantage in the surgical management of the problem The operation makes use of the deep half of these membranes, whether part of the unaltered cyst cavity, abscess cavity or fistulous channel Buie further adds "If there has been no destruction by inflammation or erosive changes within the walls of the cyst or sinuses, this membrane will possess practically the same histologic structure as that of true skin and is therefore peculiarly fitted for the purposes of the operation" He leaves intact the inner wall of the cyst and its branching tracts, the skin edges are sutured to the margins of the remnant of membrane that originally enclosed the cyst, the cyst having been first unroofed and the redundant skin edges and outer half of the cyst wall having been trimmed away The floor of the cyst then becomes the external surface

Brockbank and Floyd<sup>25</sup> recommend radiant heat for fifteen minutes twice daily to keep the wound dry and to encourage epithelialization, having returned 90 per cent of 168 patients to military duty in twenty-one to twenty-eight days with complete healing

Peterson and Ames,<sup>26</sup> Van Dyke,<sup>27</sup> Henning<sup>28</sup> and Nesselrod<sup>29</sup> are all enthusiastic adherents of this method Nesselrod gives the following caution "The most annoying problem, and one which is a source of embarrassment both clinically and statistically, is the occasional failure of mid-line healing" For this, he recommends bed rest, ultraviolet-ray therapy and surgical revision of the skin edges

(To be concluded)

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In the hospital the patient was observed to be very dyspneic and after several days began to develop sacral edema and moist rales at the left base. He was given digitalis, and an electrocardiogram taken several days after the digitalis was started showed sinus tachycardia, with evidence of digitalis effect on the ST segments and T waves, but no definite diagnosis of cardiac disease could be made. His appetite was very poor, and a Levine tube was introduced into the stomach to force feedings. All physicians who saw the patient believed that he was quite ill, and one observer noted, "He is sicker than he looks." All efforts at therapy were to no avail, the patient began to vomit blood, became more dyspneic, gradually became unresponsive and expired quietly on the twelfth hospital day. The temperature had remained at normal levels throughout the hospital course.

#### DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN In brief, the Pathology Department has invited me to make a diagnosis—I would even say that they have defied me to make a diagnosis. This was a sixty-seven-year-old man, who complained of being ill for six months, with weakness and anorexia and, I should say, asitria (a loathing of food) and vague abdominal distress. A careful investigation, including physical, roentgenologic and laboratory examinations, failed to provide an adequate diagnosis or even to give a clue. There is one small clue—a series of what I call dissociated signs of some impairment of liver function. Perhaps it would be well to discuss the one positive set of signs that we have—namely, the changes in liver function. In the first place, we find that the Graham test was reported elsewhere as being normal, and yet in this hospital a brom-sulfalein test showed 38 per cent retention of dye in the serum, which is abnormal. There was urobilinogen in the urine and some bizarre-shaped red cells and stippled cells, but there seems to be very little evidence of blood destruction. The van den Bergh test was negative, and the prothrombin time very slightly elevated, almost normal, there was a depletion of the carotenoids, and some depression of the serum protein. What do these signs indicate? I cannot accept the diagnosis of cirrhosis. But it seems that, from these tests, cirrhosis of the liver certainly had been entertained as a likely diagnosis. This was reasonable because the description of the final illness clinically reads like cholemia. It sounds like liver failure—what I believe Europeans used to call cholemia.

There are two or three red herrings that cross the trail. One is the coughing of blood, and the other, the positive guaiac reactions in three stools, indicating a lesion in the gastrointestinal tract. The x-ray films did not reveal such a lesion, and yet this would again fit with the clinical impression of cirrhosis. Esophageal varices that were leaking

were considered, and this could also account for the final episode of the vomiting of blood. An alternative explanation for the stools is that the patient was swallowing sputum from the right bronchus that contained blood, and this would better explain the intermittent positive guaiac reactions in the stools.

What are some of the things that we have to consider? Let us go back to the past history. A prostatectomy was performed twelve years before admission. Did the patient have a malignant tumor that had arisen in the prostate and involved the urinary tract? I do not see any evidence on which to base such a diagnosis and so I discard it. Was it a primary malignant lesion arising in the right main bronchus? We have the signs of fluid at the right base, dullness, diminished tactile fremitus, and diminished whispered voice—in other words, not only fluid but occlusion of the bronchus leading into the right lower lobe. Apparently no x-ray films of the chest are available.

DR STANLEY M. WYMAN No, just of the colon.

DR CHAPMAN Considering the definite cardiac changes, peripheral edema and dyspnea, did the patient have some form of underlying heart disease? We are told that the electrocardiogram was normal. No one seems to have made the diagnosis of heart disease, but I seriously entertain the possibility that this man at sixty-seven had calcific aortic valves. Calcific aortic stenosis is often overlooked in the older age group, and the signs are quite variable. He had a harsh systolic murmur and an elevated blood pressure, and finally died, with some of the symptoms of congestive failure. He did not respond to treatment. In trying to put the facts together, having entertained the other possibilities, we must consider some form of heart disease.

We must also consider carcinoma of the pancreas—in the body, of course, because the stools were colored, and there is no indication that a tumor mass was felt. But we must consider a small carcinoma of the pancreas with metastases to the liver and perhaps the lung on the right side. Carcinoma of the body of the pancreas is one of the most difficult diagnoses to make on clinical grounds, and in the case under discussion, there was no pain of pancreatic distribution or other signs to indicate such a lesion.

We must think of some rare disease involving a limited area of the liver, causing dissociated signs. The only disease that I can think of is primary tumor of the liver—a hepatoma. If the patient had a primary carcinoma of the liver, we must in all likelihood suspect an underlying minor degree of cirrhosis. I believe Dr. Mallory has taught us that in primary liver tumor there is always the co-existence of some degree of cirrhosis.

DR TRACY B. MALLORY There was in all but one case in the records of this hospital

DR CHAPMAN I think that Dr Mallory will have to tell us what was wrong. I cannot say anything except a malignant tumor involving the liver because of the clues that I have mentioned. If I have to make a diagnosis, I shall say hepatoma—whether it spread into the right chest and perhaps produced fluid or whether there was a metastasis in the region of the bronchus with erosion, it is impossible for me to say. The patient may have had an underlying calcific aortic stenosis.

DR. WYMAN The examination of the colon was unsatisfactory as the record notes because of the extremely large amount of fecal material. One can outline the lower border of the liver, but the upper margin is lost. One cannot say that the liver is grossly enlarged from these films. The spleen does not appear to deform the splenic flexure, it lies in normal position. The bones show no definite evidence of destruction that I can see. I see no definite abnormal soft-tissue masses. It is impossible to exclude a lesion of the colon, however.

DR. CHAPMAN Was a gastrointestinal series done by you, with study of the second portion of the duodenum, the possibility of pancreatic involvement with tumor and ulceration being borne in mind?

DR. WYMAN No, it was done elsewhere.

DR. BRIANT L. DECKER How about a myeloma with involvement of the liver? The serum protein was in the upper limits of normal, and the albumin-globulin ratio was 1.1.

DR. CHAPMAN I have myeloma written on the border of my copy of the abstract. I thought it unlikely and that the change of protein was consistent with liver disease, and so I excluded myeloma. One has to think of it with the reversal of the albumin-globulin ratio, but as I say I prefer to let the liver take care of that.

DR. ALFRED KRANES I cannot think of a case of myeloma without anemia. I may be wrong about that. Is that correct?

DR. MALLORY Yes.

DR. GEORGE A. McLEMORE, JR. Could the high urobilinogen have been caused by the gastrointestinal bleeding?

DR. CHAPMAN I do not know, but I doubt it. That is all I can say.

#### CLINICAL DIAGNOSES

Liver failure, probably from portal cirrhosis  
Arteriosclerotic and hypertensive heart disease,  
with congestive failure

#### DR. CHAPMAN'S DIAGNOSES

Malignant tumor of liver (hepatoma?)  
Metastases to lung  
Calcific aortic stenosis

#### ANATOMICAL DIAGNOSES

*Adenocarcinoma of pancreas, with metastases to liver, lungs, left adrenal gland and serous surfaces*

Pulmonary emphysema

Hypertrophy of heart, hypertensive type

Thrombosis of segment of inferior vena cava and both common iliac arteries

#### PATHOLOGICAL DISCUSSION

DR. MALLORY Post-mortem examination showed extensive neoplasia. The pleural and abdominal cavities were both studded with minute tumor nodules. The lungs showed extensive involvement of the pleura, extending a very short way into the parenchyma of the lung, but nothing that suggested a primary tumor. The liver was small, weighing only 1500 gm., but showed a large number of very small tumor nodules. In the body and tail of the pancreas was a large mass of tumor—the only large mass that we found. The histology was entirely compatible with a primary pancreatic tumor. I do not believe there is much question about that. I still think that we have a very inadequate explanation of the peculiar laboratory findings as related to liver failure. It takes a great deal of cancer of the liver to produce any liver failure. Usually, when metastasis to the liver is extensive enough to cause liver failure, we find the organ grossly enlarged, weighing 3000 or 4000 gm. This liver was on the small side of normal. On the other hand, the total amount of tumor in proportion to the size of the persisting liver tissue was high. I suppose we must assume that the liver metastases were responsible for the liver failure. There was nothing to suggest any primary abnormality of the organ. The cells were in good shape, and there was no bile stasis, no fatty vacuolization or anything else that one could consider primary liver disease.

We did not find any evidence of calcific aortic stenosis though the heart was generally hypertrophied as in hypertension. There was a saddle thrombus of the vena cava extending into both iliac veins, but no pulmonary emboli of significant size.

DR. KRANES The laboratory findings in themselves are inconsistent. I did not believe that it was possible to have a normal cholecystogram with a bromsulphalein retention of 30 per cent. One or the other is wrong.

DR. MALLORY I think that there was a fair time interval between the two examinations.

DR. CHAPMAN Yes, the Graham test was done before he came in and the other was just before he died.

DR. JOHN STANBURY How much pleural fluid was there?

DR. MALLORY A few hundred cubic centimeters.

DR CHAPMAN Was there no gross area of erosion in the gastrointestinal tract?

DR MALLORY No, there was one small bronchus invaded by tumor, which might have accounted for the hemoptysis, but not for extensive bleeding

## CASE 34232

### PRESENTATION OF CASE

A fifteen-year-old boy entered the hospital because of a mass in the left calf

Five years prior to admission without antecedent trauma he noted the gradual onset of pain on the medial side of the left calf. It occurred only during exercise, was not severe and did not limit his activities in any way. Approximately three years before admission he noted a lump in this area, which was tender to touch. No particular motion caused pain, and there were no paresthesias. He noted that the heel of the right shoe wore out more quickly than the left. There was no weight loss or constitutional symptoms.

Physical examination showed a well developed and well nourished boy, the positive findings being limited to the left leg. There was full range of motion in the hip, knee and ankle except for dorsiflexion of the left foot, which was limited, the foot being held in about 15° of equinus. With the knee flexed the foot could be dorsiflexed an additional 10°, but it could not be brought into the normal amount of dorsiflexion, motion in plantar flexion was normal. There was no muscle weakness or sensory change. The knee jerks and ankle jerks were active and equal. The circumference of the calf was 12 cm less on the left than on the right. On inspection there was slight prominence in the region of the belly of the medial head of the gastrocnemius, and on palpation a mass could be felt in this same region, approximately 2.5 cm long and 1.5 cm wide. The mass appeared to be within or immediately beneath the gastrocnemius muscle. It was of firm consistence, nontender and not adherent to subcutaneous tissues or skin. No bruit could be heard. No lymph nodes were felt in the popliteal or inguinal regions.

The urine was normal.

X-ray examination of the leg was essentially negative.

On the second hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR JOHN A. REIDY With the information at hand we can at least decide why this boy wore his right heel out more than the left in that the Achilles tendon on the left was necessarily contracted, giving the equinus position as described in the x-ray

report. This kept the left heel from striking the ground or at least from striking the ground as firmly as the right. I venture to say that he probably had more wear on the toe and sole of the left shoe than on the right, although that fact is not mentioned. We can assume that the equinus deformity was probably due to contracture of the Achilles tendon, particularly in view of the fact that there were no changes in the foot or ankle. Motion was fairly complete except for this lack of motion in dorsiflexion, and since x-ray films of the foot are not mentioned I take it that they were normal.

We can now direct our attention, I believe, to the firm, nontender mass that lay beneath the medial head of the gastrocnemius muscle. It probably would be well to review the x-ray films.

DR STANLEY M. WYMAN I am sorry, but we do not have the films.

DR REIDY It would be worth while to know if there was a soft-tissue shadow—it might help in better localization of the lesion. If it was down the shaft distally beneath the gastrocnemius, it would present a different picture than it would if located beneath the gastrocnemius in the proximal portion in relation to the popliteal space, where there are numerous cysts, ganglions and so forth that arise from the posterior aspect of the knee joint. If the shadow were in relation to the knee joint, it might help us somewhat. The x-ray films apparently do exclude evidence of bony disease or tumor. We can therefore confine our thoughts more or less to the soft tissues.

This lesion was a chronic one, which had been asymptomatic for five years and palpable for three years. The size is mentioned as apparently remaining the same, although it may have increased. If it did, it certainly did not increase very much—2.5 by 1.5 cm is not a large lesion and can easily be obscured. The chronicity, the lack of pain and the good general health of the patient, I believe, are helpful in ruling out the possibility of any malignant tumor. Certainly, fibrosarcoma, which is one of the more common tumors in this region, would have manifested itself much more clearly and more definitely than this tumor.

Rhabdomyoma, a skeletal-muscle tumor, which I have seen in the medial head of the gastrocnemius, is a rare lesion and I doubt that it was present in this case. Certainly, it would have been more evident.

There have been reports of synoviomias removed from the region of the knee several years after the original tumor was noted. These are slowly growing tumors and could account for the symptoms in this case.

A low-grade infectious process such as tuberculosis, I think, is a remote possibility, but there is nothing to substantiate that diagnosis.

An organized hematoma or subsiding myositis ossificans could possibly have caused this difficulty. It is unlikely, however, particularly in view of the lack of trauma or changes on the x-ray films.

An angioma or aneurysm can readily occur in this region in relation to the popliteal vessel, but here again I think the tumor would have been soft, at least softer than that described, and would perhaps have caused a bruit, which is said not to have been present. Lipoma, similarly, is a soft tumor and probably would not have resulted in the irritation and pressure that caused this contracture of the Achilles tendon.

Chondroma is a possibility in that it can occur in the region of the knee joint, extend down beneath the gastrocnemius, and not cause a shadow by x-ray study, although there may be evidence of some soft-tissue distortion. That is unlikely, however, because it is such a rare lesion, as is a fibroma occurring alone. The fibroma is more likely to arise in the hand or foot than in this region.

There are other possibilities — either a Baker's cyst or a neurofibroma. Baker's cyst is an extension of the bursa that lies in relation to the semitendinous muscle and beneath the medial head of the gastrocnemius muscle and can dissect down beneath the muscle for a considerable distance. With the knee in extension this forms a dense, frequently nontender, tumor and may cause minimal or no symptoms. It is a possibility. Yet I think that a solitary, slowly growing, nontender neurofibroma, which is one of the more common tumors that occur in this region, can produce this picture, and on the basis of frequency I shall make that diagnosis.

DR. JOSEPH S. BARR: The mass was in the most prominent portion of the medial head of the gastrocnemius muscle, about 15 cm. distal to the knee joint. We did not believe that it was a ganglion or that it was related to the knee joint. The sole x-ray film taken was for the purpose of determining whether or not there was a soft-tissue mass, but

we could not see any. The mass was definitely palpable in or beneath the gastrocnemius muscle. Some years ago I had a patient, a boy about the same age, who had a tumor in this location that proved to be a hemangioma. The tumor in the case under discussion had no bruit and was hard and firm. I was a little indefinite in my preoperative diagnosis, finally settling for a tumor of the gastrocnemius muscle.

#### CLINICAL DIAGNOSIS

Tumor of gastrocnemius muscle, ? hemangioma

#### DR. REIDY'S DIAGNOSIS

Neurofibroma

#### ANATOMICAL DIAGNOSIS

*Cavernous hemangioma of head of gastrocnemius muscle*

#### PATHOLOGICAL DISCUSSION

DR. BARR: The tumor, which infiltrated the whole medial head of the gastrocnemius, was spindle shaped and quite firm. The tumor infiltrated the muscle and had no capsule, it involved at least half the medial head of the muscle. The whole of the medial head of the gastrocnemius muscle was excised.

DR. REIDY: Did you make a diagnosis on the gross specimen?

DR. BARR: I could not have, although we called Dr. Castleman to see it and he called it a hemangioma grossly. I believe that was the final diagnosis. It was a solid tumor with large blood vessels infiltrating into it. It was so solid that I questioned the diagnosis.

DR. TRACY B. MALLORY: Microscopical sections showed a characteristic cavernous hemangioma. The tumor was surrounded by a considerable degree of inflammatory reaction. The hardness may have been due to inflammation rather than tumor.

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## ACUTE LEUKEMIA PRESENT AND FUTURE

IN an article published elsewhere in this issue of the *Journal* it is pointed out that the parenteral administration of certain folic acid antagonists is not infrequently followed by clinical and hematologic remissions in children with acute leukemia. The authors very properly stress the fact that these remissions, though somewhat prolonged, must not be regarded as cures.

Many years ago the hope was implied that acute leukemia was a potentially curable disease.<sup>1</sup> This hope and this belief stemmed from the undoubted fact that a moribund patient with unquestionable, acute leukemia went into a prolonged and complete remission after the parenteral administration of what was assumed (probably erroneously) to be adenylic acid. The remission was, however, almost certainly spontaneous, and the original disease re-

appeared in an explosive manner some five months later. In a very short time the patient was dead.

Subsequently a series of cases with acute leukemia of one sort or another with dramatic remissions of considerable duration was reported in the *American Journal of Cancer*.<sup>2</sup> Individual reports of similar remissions have appeared in standard medical journals from time to time, and still other patients have been seen but not reported. In one case a remission lasted approximately thirteen months. Some of these remissions appear to be truly spontaneous, occasionally they follow the subsidence of an acute infection. Of the 5 cases reported by Farber et al. initial remissions of this type occurred in 2.

Therefore, the possibility of a spontaneous remission must be entertained whenever a patient with acute leukemia becomes apparently well from both a clinical and a hematologic point of view. Yet so far as is known practically all such patients have subsequently died in relapse. Of the extremely rare case in which the patient did not die it may be said that the original diagnosis was incorrect.

Precisely what the bone marrow showed in these cases during the remission is not known, but as all lymphadenopathy and splenomegaly disappeared and the peripheral blood picture became entirely normal in all respects it may be assumed that the bone marrow in like manner and to like degree became normal.

This, then, is the first point: it is well known that spontaneous remissions—complete and of considerable duration—may occur in acute leukemia. It is not argued that the remissions referred to in the article under consideration were, in fact, spontaneous. It is simply pointed out that such remissions have occurred.

The second point is this: when the parenteral administration of a substance, of whatever nature, is followed by remission in leukemia one should be extremely cautious before one even implies that a true cure might result. The physician experienced in the care of leukemic patients and versed in the pitfalls of experimental work will scarcely be led astray. The practicing physician who does not specialize may grasp at this straw and overplay his hand. Believing that the earlier a case is treated the greater is the chance of success, he may treat patients whose

blood picture is suggestive of but not diagnostic of acute leukemia. And the layman — he who reads the daily press, which is no proper medium for the announcement of therapeutic measures still in their experimental stage — will not only grasp at the straw but also perhaps twist and turn even the most cautious expressions to his own supposed advantage. He may fail to distinguish between 'arrest' and 'cure', and he may brush aside as improbable or inconsequential the third point with the introduction of new therapeutic measures, even those of proved value, the beneficial effects stand prominently in the foreground and the deleterious and occasionally fatal side effects are either unrecognized or minimized. Such is the story of aminopyrine, arsenic for the treatment of leukemia, and sulfonamides and latterly folic acid.

There is some evidence, as yet unpublished, that the administration of aminopterin may be followed by refractory pancytopenia, and a similar sequence of events might follow the use of newer compounds as yet unsynthesized. It may be argued that such side effects as may occur in the treatment of acute leukemia with folic acid antagonists may be regarded as unimportant in view of the practical certainty of death in that disease. Yet whether these side effects may in themselves be fatal or permanent is not yet known, and, more important, the positive diagnosis of acute leukemia is not always easy. Physicians of international fame have been known to be wrong in its diagnosis. This being the case, it is possible that those who read the *Journal* might similarly be in error.

Clinical investigation must not be limited, and the early publication of experimental work should not be delayed once competent and unbiased observers believe the work to be well founded. It is proper and necessary, however, to be cautious to a fault.

The experimental data briefly and guardedly presented in this issue shed new light on the problem of leukemia, and we may, now, with some justice hope that aminopterin or some substance related to it, as yet unsynthesized, will afford a substantial basis for real hope in this now hopeless disease.

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## MENTAL HEALTH AND WORLD CITIZENSHIP

The International Congress for Mental Health, to be held this summer in London, will have the formation of a world federation for mental health as one of its most important objects. The subject for discussion at this world congress — Mental Health and World Citizenship — will be broken down into five main headings: problems of world citizenship and good group relations, the individual and society, family problems and psychologic disturbances, organization, training and propaganda in planning for mental health, and mental health in industry and industrial relations.

To obviate the possibility of each group discussing its topic and arriving at its conclusions quite independently of the others — as might be the case if 'specialists' only took part in the discussions — mixed committees have been set up for the consideration of each subject. These committees will be composed of a variety of elements — psychologists, psychiatrists, sociologists, educators and anthropologists. Co-operating in plans for the Congress have been Dr. Brock Chisholm, executive secretary of the interim commission of the World Health Organization, and Dr. Julian Huxley, director general of UNESCO — the United Nations Educational, Scientific and Cultural Organization.

Dr. Chisholm, in a short paper published in *Surrey Graphic* in October, 1947, outlined the world's need for a supreme effort in the direction of more universal mental health. Man, in a physical sense, is becoming the master of his environment. The material obstacles to survival he has been slowly conquering, one by one — the hazards of climate, of inadequacy in food supply, of disease. The really great obstacle that remains is man himself with his highly developed intellect that he cannot use effectively because of his neurotic fears, his prejudices, his fanaticisms, his unreasoning hates, and equally unreasoning devotions.

This, paradoxically, is today the great threat to man's survival in a world that he has otherwise tempered to his needs — the presence of other men of other races, of other creeds, of other ideologies in

that world, and their inability to live in harmony together

So great a control has man today over various environmental situations that a few men of ill will may obtain the power of affecting the destinies of millions. A single pyromaniac may destroy a forest that has been a century in growing, a small nation may have the means of plunging a great one into chaos.

And so there is present the impelling need, the need above all others of finding a scientific, factual approach to man's difficulties, of bringing him to mental health and a mature viewpoint where he will have the power and the desire

*To strive, to seek, to find, and not to yield*

## THE MASSACHUSETTS CANCER PROGRAM

THE paper by Dr. George L. Parker on the Pondville State Cancer Hospital, which appears elsewhere in this issue of the *Journal*, brings memories to those of us who can say, "All of it I saw, some of it I was."

In gazing at the panorama of twenty years of cancer-control activities, one cannot but feel the absence of those members of the Massachusetts Medical Society who are no longer with us, but whose efforts aided in building the Massachusetts cancer program. Among them may be mentioned Thomas Almy, George H. Bigelow, Orrin C. Blair, Walter P. Bowers, Martin M. Brown, J. Forrest Burnham, Farrar Cobb, Francis G. Curtis, Robert B. Greenough, Thomas P. Hennessey, William T. Hopkins, Ernest L. Hunt, George A. Leland, Edward D. Leonard, G. Forrest Martin, William J. Pelletier, Charles H. Richardson, Walter Sawyer, Halbert G. Stetson, James S. Stone, Frederick Thompson, William L. Tracy and Philemon E. Truesdale.

To these and to others, the Massachusetts Medical Society, the citizens and the Department of Public Health owe much. The farsightedness, enthusiasm and willingness of these pioneers to devote time and energy to cancer control resulted in a program that has received nation-wide recognition.

In reviewing the accomplishments of the Program one remembers the establishment of the diagnostic clinics, the opening of Pondville Hospital, the inauguration of cured cancer clinics, the survey on

cancer and other chronic diseases, followed by the publication of the results in book form, the organization of the co-operative cancer-control committees in every town and city in the Commonwealth, which began in 1935 and extended over a period of years, the teaching clinics for the medical profession, the opening of the cancer wing at Westfield State Sanatorium, the Cancer Manual for Practitioners, sent free to every physician in the Commonwealth, the utilization of the Massachusetts Program for training representatives from other states and countries in cancer control, *The Procedural Analysis of the Compilation of Cancer Data for Statistical Uses in the Massachusetts Department of Public Health Cancer Control Program*, published by the United States Public Health Service and distributed to health departments throughout the United States, the surveys to evaluate cancer education, and the experiment on cancer education in the schools of Lynn and Malden. These activities and others have contributed to make the Massachusetts cancer program the pattern for cancer programs in this country and abroad.

Diagnostic cancer clinics are functioning in eighteen strategic points throughout the Commonwealth. At these clinics, persons with suspected cancer are examined and then returned to their physicians with a statement of whether a malignant tumor was found. In the early years of the program the majority of the patients came as the result of newspaper publicity, but at the present time nearly 90 per cent of them come on the advice of local physicians. Uniform records are kept in all eighteen clinics, and follow-up observation is maintained from the diagnosis of cancer until death. The long-term follow-up study of more than 20,000 patients with cancer is one of the unique features of the program. Of the cancer patients who were seen in 1927, 2 per cent are lost, 11 per cent are still alive, and the remainder are dead.

At the Tumor Diagnosis Laboratory tissue is examined as a free service to any physician in the Commonwealth. The increasing number of specimens submitted by the profession is an indication of the value of this service.

The dissemination of information regarding cancer has been an integral part of the Massachusetts

cancer program. In a nation-wide Gallup Poll held in 1939, only about half the persons interviewed believed that cancer was curable. A few years later, a similar result was found to exist in several Massachusetts cities. Within the past year, professional surveyors visited seven Massachusetts cities, including some of those surveyed earlier, and found that approximately 75 per cent of the people were aware of the curability of cancer. The educational work of the Department of Public Health is done mainly through committees in local communities striving to furnish information through public meetings, distribution of pamphlets, school programs and other means. Recently, the educational program has become a joint effort of the Department of Public Health and the American Cancer Society, Massachusetts Division, Incorporated. These two organizations, working together, should accelerate cancer education.

Throughout the period of the program, statistical studies have been made to measure improvements, to ascertain weaknesses, to evaluate clinic procedures and to determine factors dealing with the etiology of the disease. Among the more recent studies is one to determine the practicability of furnishing the Papanicolaou diagnostic test for vaginal smears to the entire medical profession. This study, financed by the Commonwealth Fund, is now in its third year, and although the study will not be completed for three more years, a few cases have been found in which a positive vaginal smear was the only indication of a uterine cancer. Another important study that has been completed recently deals with the changing cancer death rate, giving consideration to each site separately. Whereas for some years it was noted that there was a downward trend in cancer among women and that this trend occurred in Massachusetts earlier than in other parts of the country, the behavior of the trends for individual sites of cancer have been studied only recently. Even though the general trend of the cancer death rate for women is downward, certain sites, such as the lung, pharynx and ovary, show upward trends. The downward trends for cancer of the skin, mouth, stomach, uterus and perhaps breast are sufficiently great to influence the trend of the total cancer rate for females, but the downward trend

for mouth, skin and stomach among males is not sufficiently great to offset the sites with upward trends.

At the Fourth International Cancer Congress, held in St. Louis, the Department of Public Health reported on an interesting finding about half the women with cancer of the cervix had been married under the age of twenty, contrasted with a rate of about 18 per cent of early marriages in the general population. A large part of the paper was devoted to a discussion of this phenomenon.

The fourth part of the program is hospitalization. This has been so admirably discussed by Dr. Parker that little more need be added, except to decry the fact that many empty beds are to be found in this institution, owing to a lack of personnel. With the great demand of cancer patients and with the present limitation of facilities in general hospitals, it seems deplorable that less than a third of the beds in Pondville are being used. Every effort should be made to assist the superintendent and the staff in their effort to excel the prewar status of this hospital.

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#### SANDERS COLLEGE

The third postgraduate lecture course, presented by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health in Sanders Theater, Cambridge, completed its annual term on May 5. The statistics here presented well justify the term "Sanders College" that has been applied to the course.

Between March 8 and May 5 ninety-six lectures were given in eighteen sessions. The total registration exceeded 1300, over a hundred more than in 1947, the gross attendance was 7400, with an average of 411 at each session. The sessions on allergy and psychiatry, the least well attended, drew each an audience of approximately 250 "students." A crowd of 850 thronged the sessions on cardiovascular diseases.

Congratulations are due to the Committee on Postgraduate Instruction, which arranged the program, as well as to the Hub of the Universe, where an indifference to learning can hardly be said to have manifested itself.



## MEDICOLEGAL ABSTRACT

**Liability for Malpractice—Duty of physician to explain cause of injury occurring during treatment** Many doctors have had the experience of a patient dying or being injured under circumstances that according to the ordinary course of events suggest that the doctor was negligent. He may be able to account for his own conduct and feel sure that it was proper even though he cannot explain how the injury occurred. A recent California decision makes it seem prudent for him to do whatever he can to determine the cause of the injury lest he be held responsible.

In an earlier California case (*Ybarra v Spangard*), in which the court, disposing of a contention that a plaintiff could not recover when he failed to show more than that after an appendectomy he had awakened with a painful shoulder, which subsequently resulted in an atrophied and paralyzed arm, stated

We merely hold that where a plaintiff received unusual injuries while unconscious and in the course of medical treatment all those defendants who had any control over his body or the instrumentalities which might have caused the injuries may properly be called upon to meet the inference of negligence by giving an explanation of their conduct.

This holding was based upon what is referred to as the doctrine of *Res ipsa loquitur*; that negligence is presumed when a plaintiff is injured by an instrumentality entirely within the defendant's control under circumstances that would not ordinarily arise unless someone had been negligent. The more recent California case clarifies the extent to which the defendants must go in making an explanation of their conduct under such circumstances.

A surgeon planned to remove a wart from a patient's nose after anesthetizing the patient with a nonexplosive gas, and then to remove the tonsils under ether anesthesia. The patient was completely anesthetized with nitrous oxide and oxygen, and the wart was removed with an electric needle. After the surgeon had finished removing the wart and was cauterizing the wound with the electric needle there was a "flash" and a "pop" about 6 inches above the patient's face. As a result of this accident the patient suffered contusions to the left cheek and left eye, bled profusely from the nose and mouth and was hospitalized for fifteen days. The doctor testified that at the time of the "flash" and "pop" the nitrous oxide and oxygen had been turned off and that the ether had not yet been turned on, that to give ether would have required the switching of the apparatus, and that the apparatus had not been switched. The doctor described in detail what he was doing before and at the time of the accident. However, neither the doctor nor the anesthetist could ac-

count—and neither attempted to account—for the "flash" and the "pop" that caused the injuries. The director of the anesthetic department of the defendant's hospital was called as a witness by the surgeon. He qualified as an expert on anesthesia, and when asked his opinion as to the cause of the "flash" and the "pop," he made the following statement:

I think that the strongest possibility From the information, I suspect My opinion would be, one probable likelihood would be, from contaminating substance in one of the tanks, some foreign substance

The nurse in charge of surgery testified that the breathing tube leading from the container to the patient's face had been properly washed with soap and water immediately before its use. The expert on anesthesia admitted that it was possible for a chemical laboratory to test nitrous oxide to determine if it were contaminated. It did not appear whether the defendants had made such a test of the nitrous oxide remaining after the operation. The jury rendered a verdict in favor of all the defendants.

On appeal the plaintiff contended that the jury should have been directed to find for her, and the upper court reversed the judgment and ordered a new trial, saying

The showing here goes farther than the establishment of a mere prima facie case under the doctrine of *res ipsa loquitur*. Not only is there a prima facie showing that the accident is one which in the ordinary course of events would not have happened if defendants had used due care but the defendants themselves have established the "possibility" or "probability" that they used an impure and, under the circumstances, dangerous anesthetizing agent. That agent, the nitrous oxide, was at all times concerned in the exclusive possession and control of defendants. If such nitrous oxide was not impure, it was in the power of defendants to prove the fact, if it was impure, as their evidence suggests, then the burden was on them to account for the impurity. The defendants offered to prove neither that the gas was pure nor that they were not responsible for its impurity. We are constrained to the conclusion that in a *res ipsa loquitur* case where, in addition to the prima facie showing of negligence, it is admitted or appears without dispute that the defendant has it in his power to produce substantial evidence material to the issue of negligence but fails to do so, it must be presumed that such evidence, if produced, would have been adverse to defendant, and under such circumstances the evidence is insufficient to support a verdict for the defendant and plaintiff is entitled to a directed verdict.

This is not to say that a defendant in a *res ipsa loquitur* case has the burden of proving himself free from negligence. It is not to say that a defendant must in every such case produce evidence of the actual cause of the accident. It is not to say that the question of the sufficiency of a defendant's explanation—or, if he cannot explain, the sufficiency of his evidence of due care and of impossibility of explanation—is not ordinarily for the jury. The general principle is, as stated by this court in 1919 (*in denying a hearing in Bourguignon v Peninsular Ry Co*, 40 Cal App 689, 694-695 [181 P 669]) "that where the accident is of such a character that it speaks for itself, as it did in this case, the defendant will not be held blameless except upon a showing either (1) of a satisfactory explanation of the accident, that is, an affirmative showing of a definite cause for the accident, in which cause no element of negligence on the part of the defendant inheres, or (2) of such care in all possible respects

as necessarily to lead to the conclusion that the accident could not have happened from want of care but must have been due to some unpreventable cause although the exact cause is unknown. In the latter case, inasmuch as the process of reasoning is one of exclusion the care shown must be satisfactory in the sense that it covers all causes which due care on the part of the defendant might have prevented."

"The defendants have not met either test above stated. They did not show a definite cause for the accident unless it was the use by them of an impure or contaminated anesthetizing agent. Such definite cause is not shown to possess no element of negligence on their part although evidence material to this issue was available to them. And in respect to an exclusionary showing as has been pointed out above the evidence fails in several respects to support a conclusion that the accident could not have happened from want of care. It fails in this regard not because of any showing of impossibility of proof but rather, because defendants having the ability to produce it chose not to do so. It is therefore apparent that upon any reasonable view of the record and giving effect to the rules of law hereinabove discussed the verdict of the defendants cannot be sustained.

In a vigorous dissent by three of the seven justices, it was stated

Under the doctrine of *res ipsa loquitur* the majority opinion in effect imposes upon a defendant even more than the burden of proving that he was not negligent. It imposes the burden of proving the actual cause of the accident, for that is the only practical way under the opinion that defendants can show that they were free from fault. The imposition of such a burden necessarily involves the adoption of a rule on grounds of policy that persons in attendance during an operation must explain not only their own conduct, but the conduct of any other person, such as a manufacturer of anesthetics, who might conceivably be responsible for the accident, as well as the forces of nature that brought it about. Such a rule would impose upon doctors, nurses, and members of hospital staffs absolute liability for unusual accidents that they cannot explain and might discourage their attending operations. A person about to undergo an operation is generally aware that there may be unforeseeable dangers incident thereto. He is entitled to an explanation of the conduct of the persons attending the operation, but he cannot reasonably expect them to be insurers of his safety.

Under the majority opinion the defendants would not have to prove the cause of the injury if they showed that it had not been caused by anything that due care on their part might have prevented. However, it is difficult to determine from the majority opinion in what respect the majority considered the defendant doctors negligent. The court objected to their failure to produce evidence that they might have produced regarding the cause of the injury, but the evidence seemed to refer to possible negligence on the part of the manufacturers of the nitrous oxide or on the part of the hospital in its manner of storing it.

These details of evidence have no direct bearing on other cases involving different facts, but the prudence of determining the actual cause of an injury occurring under circumstances that otherwise suggest negligence on the part of the doctor is plainly indicated. (*Dierman v Providence Hospital, California Advance Reports* 31 A. C. No. 5, January 9, 1948, *revising* 79 A. C. 374.)

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH CONTAMINATED AMPOULES IN CIRCULATION

A communication has been received from the Federal Food and Drug Administration to the effect that three codes of Obeto Ampuls, manufactured by Ziegler Pharmacal Company, Buffalo, New York, have been found to contain viable yeast or bacteria. The known questionable code numbers are

7436

7275

7085

Other codes are now being checked

It is believed that this product has gone directly to physicians. If physicians have in stock any ampoules bearing the three code numbers referred to above, they are requested to return all unused stocks to the manufacturer immediately.

If it is subsequently determined that other codes of this product have been found to be contaminated, physicians will be advised accordingly.

## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL 1948

DISEASE*	RÉSULTÉ		
	APRIL 1948	APRIL 1947	SEVEN YEAR MEDIAN
Cholera	0	0	0
Chicken pox	1971	2667	1751
Diphtheria	18	40	15
Dysentery	1086	1053	1073
Dysentery bacillary	12	7	5
German measles	130	102	123
Gonorrhea	254	332	312
Oral gonorrhea	0	1	0*
Oral gonorrhea, venereal	1	2	3*
Lymphogranuloma venereum	3	2	2
Malaria	5950	1736	4012
Measles	2	6	16
Measles, meningoencephalitis	1	7	3
Measles, Pfeiffer-Bacillus	1	2	6†
Measles, pneumococcal	0	0	0†
Measles, staphylococcal	0	1	1†
Measles, streptococcal	1	1	0†
Measles, other forms	4	2	4†
Measles, undetermined	2615	1131	1483
Mumps	114	203	338
Pneumonia, lobar	0	0	1
Poliomyelitis	16	16	6
Salmonellosis	213	486	1422
Scarlet fever	256	301	419
Syphilis	259	261	232
Tuberculosis, pulmonary	8	17	17
Tuberculosis, other forms	3	2	2
Typhoid fever	3	2	4
Undulant fever	3	2	2
Whooping cough	181	499	768

\*Four year median.

†Six year median.

### COMMENT

Diseases with incidence above the seven year median are chicken pox, diphtheria, bacillary dysentery, measles, mumps and salmonellosis.

Diseases with incidence below the seven-year median are German measles, lobar pneumonia, scarlet fever and whooping cough.

Diphtheria has shown a lower incidence six other times during April. Constant effort toward prevention is still needed. Mumps shows the highest incidence for April since 1915. Measles shows the fourth highest April incidence. Whooping cough is at the lowest level for April since 1915.

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Athol 1, Boston, 9, Hanover 1, Haverhill 1, Lowell 1, Natick 1, Revere 1, Waltham 2, Weymouth 1, total 18.

Dysentery, bacillary, was reported from Worcester, 12, total, 12  
 Encephalitis, infectious, was reported from Cambridge, 1, Milton, 1, total, 2  
 Malaria was reported from Boston, 1, Braintree, 1, Malden, 1, total, 3  
 Meningitis, meningococcal, was reported from Dracut, 1, Ware, 1, total, 2  
 Meningitis, Pfeiffer-bacillus, was reported from Rockport, 1, total, 1  
 Meningitis, pneumococcal, was reported from Framingham, 1, Somerville, 1, total, 2  
 Meningitis, other forms, was reported from Quincy, 1, total, 1  
 Meningitis, undetermined, was reported from Haverhill, 1, Melrose, 1, Wakefield, 1, Waltham, 1, total, 4  
 Salmonellosis was reported from Attleboro, 1, Beverly, 2, Boston, 2, Brockton, 1, Holyoke, 2, Lawrence, 1, Millbury, 1, Natick, 2, Peabody, 1, Salem, 2, Worcester, 1, total, 16  
 Septic sore throat was reported from Attleboro, 1, Boston, 4, Brockton, 1, Cambridge, 1, Dartmouth, 1, Greenfield, 1, Medford, 1, Milton, 1, total, 11  
 Trichinosis was reported from Fall River, 1, Hanover, 3, Pembroke, 1, total, 5  
 Typhoid fever was reported from Boston, 2, New Bedford, 1, total, 3  
 Undulant fever was reported from Boston, 1, Weston, 1, Weymouth, 1, total, 3

## MISCELLANY

### NEW VETERANS HOSPITAL SITE

Acquisition of a new 15-acre site in Boston for a thousand-bed Veterans Administration general medical and surgical hospital has been approved by President Truman and the Federal Board of Hospitalization

This tract of land, in Jamaica Plain, is bounded by Heath Street, South Huntington Avenue, Kenney Street and the Jefferson Public School playground

### BLUE SHIELD EXTENSION

The House of Delegates of the Connecticut State Medical Society has voted to establish a prepayment medical-care plan patterned after Blue Shield in Massachusetts

Medical service plans have also been established recently in Minnesota and in Chicago, and South Carolina has passed an enabling act permitting the formation of a Blue Shield type of prepayment plan in that state.

## CORRESPONDENCE

### SALT-FREE BREAD

*To the Editor* The increasing use of sodium-poor diets for patients with cardiovascular disease raises the problem of finding a baker who will prepare salt-free bread for the use of such patients. I have found Albert Duplain, of 61 Albion Street, Boston, to be most co-operative in making up batches of French-type bread without salt or shortening. No doubt other bakers will show similar willingness to make salt-free bread, although the limited demand will not offer them much financial incentive.

ROBERT W. BUCK, M.D.

5 Bay State Road  
 Boston 15

## NOTICES

### ANNOUNCEMENT

Dr James A. McLaughlin, of Marshfield, announces the opening of an office at 17 Leyden Street, Plymouth, for the practice of internal medicine.

## JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
 Lecture Hall, 9-10 a.m.

### MEDICAL CONFERENCE PROGRAM

Wednesday, June 9 — Further Observations in Hemolytic Anemia. Dr. William Dameshek.

Friday, June 11 — Histochemical Problems in Biology and Medicine. Dr. Edward W. Dempsey.

Wednesday, June 16 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, June 18 — Cardiospasm. Dr. Franz J. Ingelfinger.

Wednesday, June 23 — Myelography. Dr. Samuel Blank.

Friday, June 25 — The Treatment of Migraine. Dr. John R. Graham.

Wednesday, June 30 — Experimental Studies on the Restoration of the Circulation. Dr. Allan D. Callow.

On Tuesday and Thursday mornings from 9 to 10, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On the second and fourth Friday afternoons of each month, therapeutic conferences will be held from 2 to 4 with round-table discussion. Dr. R. P. McCombs, moderator. Dr. Merrill Sosman will conduct x-ray conferences from 4 to 6. On Saturday mornings from 9 to 10 clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12 to 1.

All exercises are open to the medical profession.

## NEW ENGLAND PEDIATRIC SOCIETY

The spring meeting of the New England Pediatric Society will be held in New Haven, Connecticut, on Wednesday, June 9.

### PROGRAM

*At New Haven Hospital (789 Howard Avenue)*

12 m. to 1 p.m. Pediatric Conference

1 to 2 p.m. Luncheon

2 to 4:30 p.m. Scientific Program

*At New Haven Medical Association (364 Whitney Avenue)*

5 to 6 p.m. Social Hour

6 p.m. Dinner

7 p.m. Multiple Birth in Colonial Times. Dr. Ernest J. Caulfield, of Hartford, Connecticut.

## AMERICAN ASSOCIATION OF MEDICAL MILK COMMISSIONS, INC.

A meeting of the American Association of Medical Milk Commissions, Inc., will be held at the Avalon Hotel, Waukegan, Wisconsin, from June 18 to 21. Dr. Tom D. Spies, of Birmingham, Alabama, will be the principal speaker at the scientific meeting on June 19.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 10

#### FRIDAY, JUNE 11

\*9:00-10:00 a.m. Histochemical Problems in Biology and Medicine. Dr. Edward W. Dempsey. Joseph H. Pratt Diagnostic Hospital.

\*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Diagnostic Hospital). Joseph H. Pratt Diagnostic Hospital.

#### MONDAY, JUNE 14

\*12:00 m. Clinicopathological Conference. Margaret Jewett Hall. Mt. Auburn Hospital, Cambridge.

#### TUESDAY, JUNE 15

\*12:00 m. X-ray Conference. Margaret Jewett Hall. Mt. Auburn Hospital, Cambridge.

\*12:15-1:15 p.m. Clinicoradiogenetological Conference. Peter Bent Brigham Hospital.

(Notices concluded on page xiii)

## NOTICES (Concluded from page 820)

\*1:30-2:30 p.m. Pediatric Rounds. Barnham Memorial Hospital for Children Massachusetts General Hospital.

Wednesday June 16

\*9:00-10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Barry and H. E. MacMahon, Joseph H. Pratt Diagnostic Hospital.

\*12:00 p.m. Grand Rounds and Clinicopathological Conference. (Children's Hospital) Amphitheater Peter Bent Brigham Hospital.

\*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater Children's Hospital.

\*Open to the medical profession.

June 3-6. American Orthopaedic Association. Page 614 issue of May 6.  
June 7-10. National Gastroenterological Association. Page 455 issue of March 25.

June 8. New England Society of Anesthesiologists. Page 754 issue of May 20.

June 9. New England Pediatric Society. Page 820.

June 9-30. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Page 820.

June 11. Harvard Medical School Class of 1898. Page 722 issue of May 13.

June 14-16. American Neurological Association. Page 582, issue of April 15.

June 16-18. New England Health Institute. Page 754 issue of May 20.

June 17-20. American College of Chest Physicians. Page 455 issue of March 25.

June 18-21. American Association of Medical Milk Commissioners Inc. Page 820.

June 20. American College of Radiology. Page 722 issue of May 13.

June 20. National Conference of County Medical Society Officers. Page 754 issue of May 20.

June 20 and 21. American Radium Society. Page 543 issue of April 6.

June 21 and 22. American Society for the Study of Sterility. Page 341 issue of March 11.

June 23. University of Pennsylvania Medical Alumni Society. Page 678, issue of May 6.

June 25 and 26. Christian Medical Society. Page 492 issue of April 1.

June 28-30. American Academy of Pediatrics. Hotel Schroeder Milwaukee, Wisconsin.

July 6-24. Students International Clinical Congress. Page 455 issue of March 25.

July 12-17. First International Poliomyelitis Conference. Page 36, issue of January 1.

August 11-21. International Congress on Mental Health. Page 344 issue of March 4.

August 21-26. International Society of Hematology. Page 419 issue of March 18.

August 26-28. American Association of Blood Banks. Page 420 issue of March 18.

September 7-11. American Congress of Physical Medicine. Page 582, issue of April 15.

September 13-15. American Academy of Pediatrics. Olympic Hotel Seattle Washington.

Advertisement



From where I sit  
by Joe Marsh

## Three Mighty Important Ideas

*Maybe you read, where a great encyclopedia has sorted all basic ideas into a few select groups Under the letter "T" they have*

### Temperance—Truth—Tyranny

Sounds like a funny combination And to philosophize a little, notice that Truth is in the center—between Tyranny and Temperance

*Now and then you hear folks criticize temperate people who enjoy a moderate glass of beer who talk about "two beers" getting someone into trouble, and claim "There ought to be a law!"*

Then Truth steps in between, and points out that two beers never got anybody into trouble—and that somebody's trying to distort the facts No, there shouldn't be a law—there should be Truth

*From where I sit, those ideas are arranged just right Temperance on one side, Tyranny on the other—and Truth in the middle—seeing that Tyranny never encroaches upon Temperance*

Joe Marsh

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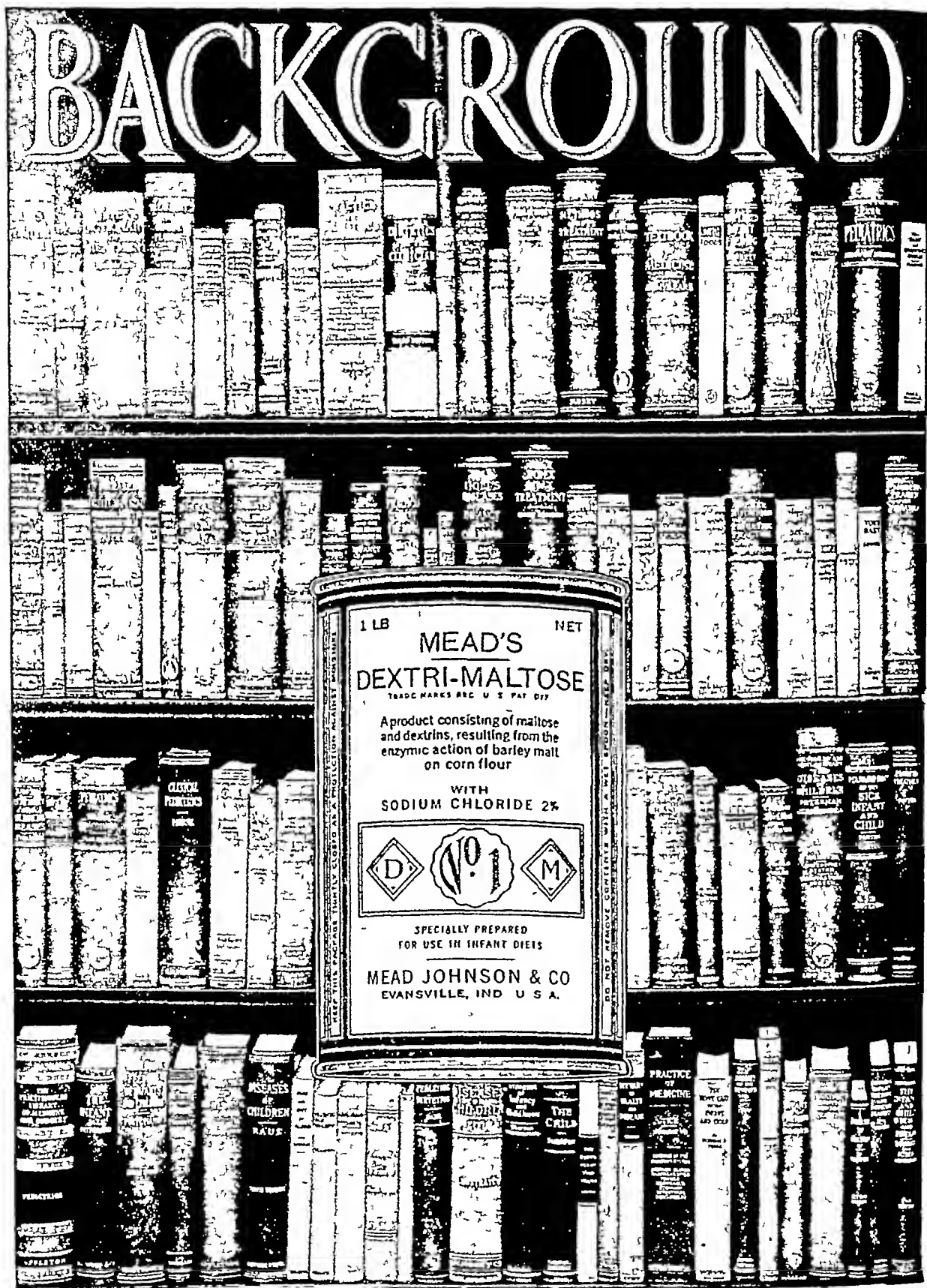
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# The New England Journal of Medicine

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Number 24

## THE SHATTUCK LECTURE

### SURGERY IN THE AGED\*

C STUART WELCH, M.D.†

BOSTON

THE honor of delivering the fifty-ninth Shattuck Lecture has been given me, I take it, because of my recent appointment to the professorship of surgery in Tufts College Medical School. This pleasant and honorable task is a great responsibility, and I approach it realizing the difficulty I shall have in upholding the high tradition left by the long line of distinguished physicians who have preceded me.<sup>1</sup> The subject for this evening is surgery in the aged, a topic that to some degree will give consideration to an aspect of the diseases of the inhabitants of the Commonwealth in keeping with the suggestion of Dr. George Cheyne Shattuck, whose bequest founded this lecture.<sup>2</sup> The substantial yearly increase in the proportion of elderly people in the population of this country that has been going on since Dr. Shattuck's time reflects the accomplishments of medical people as they have turned their efforts to science and to practice. Medicine may take great credit among the biologic sciences, for the reduction in infant mortality and the control of infectious diseases have allowed more of the newborn to reach mature age.<sup>3</sup> These are the principal factors responsible for more and more people entering the aged group. Data from the annual report on vital statistics of Massachusetts reveal that one hundred years ago 80 per cent of deaths occurred in persons before they had reached their fortieth birthday. Today only 14 per cent of deaths are recorded in this relatively young group of people (Fig. 1). During the same period we have not made commensurate strides in the control of the diseases of maturity in later life. We are struggling with these problems now. The man beyond seventy years of age today is probably no better a physical organism than his counterpart a hundred years ago, but there is no doubt that much more effective treatment for his ills is available today than

existed in 1848. New England ranks first among the various regions of this country as the home of the aged, and Massachusetts is second only to the state of Vermont in New England for its high proportion of old inhabitants. Its longer establishment with an attending decrease in the number of young foreign and domestic settlers is beginning to demonstrate a trend toward a fixation of its population, with a concomitant increase in the aged group. The medical problems of the aged,

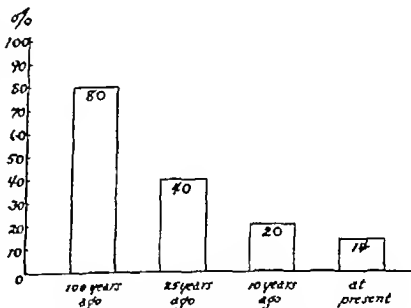


FIGURE 1. Percentage of Total Deaths Occurring in Persons under the Age of Forty Years in Massachusetts

therefore, have particular significance for the members of the Society, and since we face, according to predictions, a doubling of our aged population by 1980, the whole subject of geriatrics should assume increasing importance. Data from the census of the United States indicate that Massachusetts has approximately nine times as many people who have reached the age of fifty as it had in 1850. These 1,036,104 persons make up almost a quarter of our population (Fig. 2). Population increase alone does not account for this total figure, for there has also been a constant increase

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 25, 1948.  
†From the Department of Surgery, Tufts College Medical School, The Carney Hospital and the Joseph H. Pratt Diagnostic Hospital.  
1. Professor of surgery, Tufts College Medical School.

in the number of the elderly per one hundred persons in this state (Fig 3) Looking at the other side of the picture, we find that 42.3 per cent of our people were twenty years of age or younger in 1840 whereas only 30.7 per cent were found to be in this age group in 1940. Of greatest signifi-

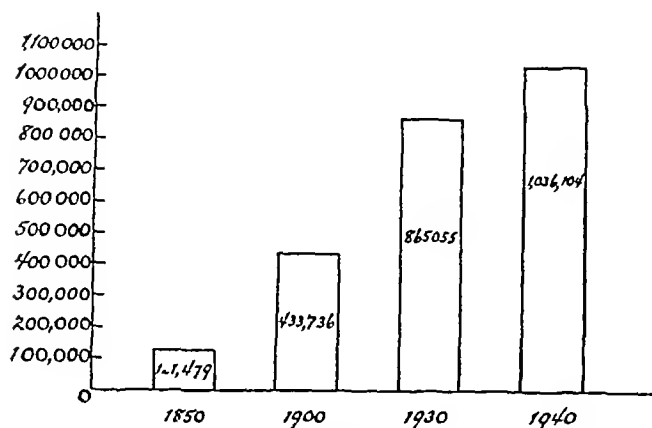


FIGURE 2 Number of Persons Fifty Years or Older in Massachusetts

cance to our discussion of surgery is the fact that today 5 per cent of the population of Massachusetts is composed of men and women who have reached or passed their three score years and ten, a proportion twice that which obtained in the year 1850. The female of the species is more numer-

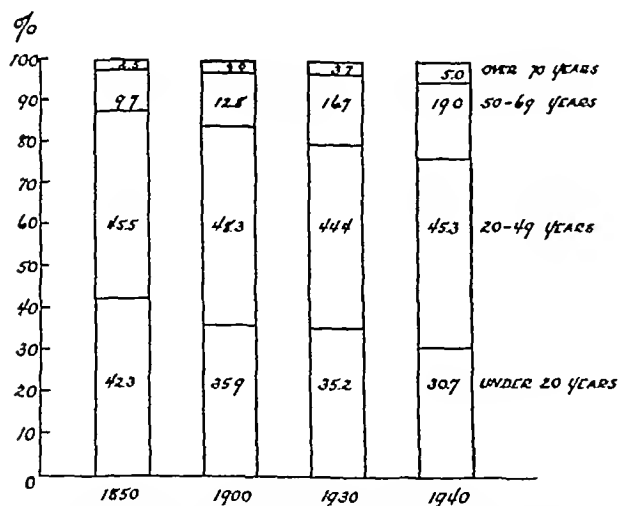


FIGURE 3 Age Distribution of Massachusetts Population

ous among the aged, and she has, each year, greater life expectancy and may expect a lower mortality from all diseases.<sup>4</sup> The aging process varies in individuals, and although a minimum of wear and tear is helpful in supporting a long and useful life, heredity probably is the greatest single factor that

works for or against a hale and hearty longevity.<sup>5</sup> It is impossible to set a standard for the beginning of old age, for each individual requires separate appraisal. The age of sixty-five is frequently used as the base line for the presentation of medical and surgical geriatric problems, but I am in agreement with Brooks<sup>6</sup> that the inclusion of persons aged sixty-five to seventy in these studies brings into the picture too large a number of patients who have only recently passed the average duration of life. As a matter of fact, in statistical studies of surgical patients that include those aged sixty-five and beyond, one finds that half or more have not reached the age of seventy but are in the age range of sixty-five to sixty-nine.<sup>7</sup> The age of seventy, therefore, seems the more critical one for presentation of the difficulties that attend surgery in patients of advanced years. I shall attempt to present a general survey of the surgical problems as they are met in this aged group. In addition, I wish to emphasize the encouraging side of the story by commenting on the progress made in surgical practice during recent years, which has brought unexpected benefit to old people and added useful years to their lives.

#### OPERATIVE SURGERY

As we review the progress made on all sides in medicine and surgery during the last twenty-five years, it would be small wonder if surgeons had not gradually accepted an increasing number of elderly patients for major surgery. With this experience has come surprising satisfaction to surgeons, who have had the pleasure of observing how well many aged patients withstand even the newer and more radical operative procedures as they are introduced. Although it is true that mortality rates are somewhat higher among these patients and much depends upon whether an emergency situation is to be dealt with, the procedures are not so prohibitive as we used to believe them to be. Numerous accounts in the literature attest to these facts.<sup>8-14</sup>

This changing scene in surgery is well demonstrated in the history of the surgical treatment of aged patients at the Carney Hospital. In 1900 only 15 persons of seventy years of age or more were operated upon in this institution, of whom over half had operations on the eyes, no abdominal surgery was done. Twenty-five years later 28 patients, or nearly twice as many as in the year 1900, were operated upon, and at that time a few more major procedures were carried out. Several hernioplasties, amputations of the leg and mastectomy procedures were performed. No resections of the stomach or colon, however, were undertaken. In 1947, not quite 25 years later again, 128 patients seventy years of age or over underwent surgery, and among them 41 had abdominal operations performed. Although it is true that the

hospital admissions had trebled at the Carney Hospital in the forty-seven years since 1900, it is obvious that the number of aged patients subjected to operations had increased out of proportion to the larger census and that more major procedures are now being undertaken. Surgical practice varies in different institutions depending upon their size, location and institutional developments in special fields. The operative work done by my colleagues at the Carney Hospital during the last five years had been generally illustrative of the problems commonly met in geriatric surgery, and I shall present their experiences to give a cross-

agency operation. Bronchopneumonia was recorded as the cause of death in 9 patients, infection in 7, massive pulmonary embolism in 4, and cerebral hemorrhage in 3. Four patients died of surgical shock. Not only is the circulatory mechanism easily embarrassed in the aged patient with peritonitis, pneumonia and sepsis but also sudden cardiac and peripheral arterial accidents are unfortunately common. Cardiovascular complications represent the *blitz* of surgery in the aged.

The average age of all patients in the series was found to be seventy-four years. In the fields of

TABLE 1 Data in 609 Operations Performed on 542 Patients Seventy Years of Age and Over\*

TYPE OF OPERATION	542 PATIENTS			609 OPERATIONS		
	NUMBER	AVERAGE AGE	DEATH IN HOSPITAL	NUMBER	DEATH IN HOSPITAL	MOR TALI TY %
Abdominal	129	74	29	140	29	20.7
Urologic	111	72	14	149	14	9.4
Ophthalmologic	67	76	2	71	2	2.8
Vascular	54	77	7	66	7	10.6
Orthopedic	37	77	4	38	4	10.5
Gynecologic (nonabdominal)	34	74	2	35	2	5.7
Breast	27	74	0	27	0	0.0
Hernia (including strangulated)	23	75	8	23	2	8.7
Head and neck (neoplasms)	21	75	0	21	0	0.0
Rectal (minor)	13	75	0	13	0	0.0
Plastic	8	73	0	8	0	0.0
Superficial infections	7	74	0	8	0	0.0
Miscellaneous	9	77	2	10	2	20.0
Totals	542	74	62	609	6	10.2
Averages			11.4			

\*Carney Hospital series.

section picture of the surgical requirements of elderly people.

In the five-year period 1943 through 1947, 609 operations were performed on 542 patients who had reached or passed their seventieth birthday in this institution of mixed public and private constituency. These data are presented in Table 1 and classified according to the type of operation that the patients underwent. The larger number of operations than patients is accounted for by stage procedures, particularly in the operations of prostatectomy and resection of the colon. More patients were subjected to abdominal surgery, although more operations were performed in the urologic field. Sixty-two of these 542 patients died in the hospital after operation, representing a total mortality of 11.4 per cent. In Table 1 the mortality rates for patients and operative procedures are separately recorded. Twenty-three patients died of cardiac failure, with renal complication in some cases, as might have been expected in this age group. Twelve patients died of peritonitis, among the group of 29 who succumbed after abdominal surgery, many of the deaths from peritonitis were among patients who required

orthopedic and vascular surgery, the average age of patients was seventy-seven years—higher than that in the other specialties. Eighty-five persons (15.7 per cent of the total) were eighty years of age or older, and 5 were in their nineties. The urologists had to deal with the larger number of patients beyond the age of eighty. Two hundred and eighty-four were females, and 258 were males. The surgery required by elderly people varies considerably from that of the young or middle-aged patient as Brooks<sup>6</sup> has pointed out. Approximately two thirds of them in our series, however, required abdominal, urologic or ophthalmologic surgery or surgery for diseases of the peripheral vessels. The major problems incurring higher mortality rates require separate discussion, for by a study of this group we may learn to recognize the obligations we face in avoiding disastrous situations that attend procrastination in our care of the aged.

#### Cancer

Twenty-eight per cent of the patients in this series were operated upon because of malignant disease. All had carcinoma except 2—1 patient of the bone, and another.



the uterus. In Table 2, the sites of these lesions are recorded. Carcinoma of the gastrointestinal tract was most commonly encountered and represented the most important division of the work in abdominal surgery. The second largest incidence of cancer was found in the patients requiring urologic surgery. Cancer of the prostate in male patients was the principal cause of a high incidence of 19.6 per cent among the elderly patients treated by the urologists. A fairly substantial number of patients have superficial or palpable lesions. Epithelioma of the face and cancer of the lip are fortunately

TABLE 2 *Cancer among 153 Patients Seventy Years of Age or Over \**

SITE	NO OF PATIENTS	PERCENTAGE OF TOTAL	DEATH IN HOSPITAL %
Gastrointestinal tract	61	39.9	29.5
Genitourinary tract	30	19.6	16.7
Breast	26	17.0	0.0
Skin, oral cavity and lip	19	12.4	0.0
Female genital tract	16	10.5	12.5
Bone	1	0.6	0.0
Total	153		
Averages		100.0	15.7

\*Carney Hospital series

easily detected and treated, and with the smaller risk entailed in the necessary operations there is little excuse for delay in proper treatment. There were 26 patients with cancer of the breast who were operated upon without any deaths in the group. Primary radical mastectomy was performed in 19, 2 additional patients had secondary axillary dissections after simple mastectomy had

TABLE 3 *Cancer Death Rates in Massachusetts for Persons Seventy Years of Age or Over*

YEAR	POPULATION	DEATHS FROM CANCER	RATE PER 100,000 DEATHS FROM CANCER
1900	84,751	476	562
1920	121,926	1269	1041
1940	216,494	2695	1245
1945	226,299	3067	1355

been done previously. In 5 cases the surgeon elected to perform simple mastectomy alone. As a general rule, it is safe to say that in almost all patients, radical mastectomy can be done with very low risk.

The cancer problem in the aged patient is becoming increasingly important. Among the causes of death for 1946 in the report on vital statistics for Massachusetts, cancer ranked second to the circulatory group in importance for persons of seventy years of age and beyond. In Table 3 the cancer death rates in Massachusetts for these persons

are recorded for several years. In 1900 there were 562 per 100,000 deaths attributable to cancer in patients seventy years of age or over. This figure had risen in 1940 to 1245 per 100,000 and had increased to 1355 for the year 1945. Thirty-nine per cent of all deaths from cancer in this state occurred among patients seventy years of age or older during 1946. Early diagnosis with adequate prompt treatment is due to the older patient as well as the younger. There has been a tendency among physicians to allow even easily treated superficial and palpable cancer to proceed to an advanced stage without treatment on the basis of the faulty reasoning that death from another cause might easily overtake the very old person before he succumbs to cancer. Almost a third (29.4 per cent) of patients with cancer in the Carney Hospital series of aged patients had superficial or palpable lesions. These were treated by surgery without incurring any mortality. Life-expectancy tables for the aged group are illuminating and should give the physician pause before he makes purely speculative decisions about these matters for his patients. Persons who live to seventy are in a group whose life expectancy is approximately nine years, and those aged eighty have an expectancy of about five years of life.<sup>6</sup>

It was not a long while ago that patients with intra-abdominal cancer were denied operation by the surgeon on the basis of advanced age alone. Now this time has passed. Certainly, when surgery is the only or best treatment for a given malignant lesion, the risk in relation to the patient's disease and his general health should assume sole importance in deciding for operation or the procedure best adapted to the situation. With the inevitability of death from cancer, fairly wide chances are often justifiable. Fortunately, the increasing demonstration of reasonable safety in operative surgery today, as well as the encouraging evidence that patients with cancer are seeking medical advice more promptly,<sup>18</sup> has given surgeons sufficient experience in the treatment of the aged patient with cancer to establish an imposing evidence that risks have been overestimated in the past. In addition it is all too true that the question of the evaluation of a patient's status is difficult. Some patients judged to be poor risks do surprisingly well, on the other hand, it must be admitted that others with greater expectations have proved disappointing.

Some may ask whether or not the larger number of patients being successfully operated upon for cancer has not increased the life expectancy in the aged population and decreased the death rate among elderly patients. Certainly, it is the individual experience of all surgeons that the life expectancy of many of their patients has been improved and that some patients have been cured. The question is difficult to answer for a number

of reasons, the first of which is that cardiac and vascular diseases greatly outstrip cancer as a cause of death in the old. The field in cancer treatment, although substantial, is too small to make a great impression on vital statistics. Secondly, the increasing number of persons who now live to the age of seventy each year and go on to develop cancer produces an ever enlarging aged population dying of this disease. These factors tend to obscure the results of our efforts in treatment. In succeeding years, perhaps, some statistical evidence may reflect the results of effective cancer treatment among the aged.

### Abdominal Surgery

Abdominal operations were attended by a higher mortality than others in the Carney Hospital series of elderly patients. This finding is a constant one in all studies of surgery in the aged. Twenty-two and a half per cent of the 129 patients whose abdominal cavity was entered died during the post-operative period. The 140 operations performed on these 129 patients are listed in Table 4. The seriousness of the disease was the principal factor influencing increased mortality. The important categories of abdominal surgery in the aged are the management of cancer of the gastrointestinal tract, urgent abdominal operations for acute conditions and surgery for gallstones.

**Cancer of the gastrointestinal tract.** Thirty-nine and nine-tenths per cent of the patients undergoing abdominal surgery had cancer of the gastrointestinal tract. Of these 61 patients only 24, or approximately 40 per cent, were found to have resectable lesions. Advanced disease with metastases was an unfortunate finding. Patients with carcinoma of the colon were more frequently admitted to the hospital with intestinal obstruction, sometimes of long duration, requiring emergency decompression operations. Many of these patients did not survive. These complicating factors made operation particularly hazardous and account, to an important degree, for a higher mortality and lower resectability than obtains among younger patients. It is common knowledge that symptoms in elderly people are frequently neglected by themselves and their associates, and are interpreted as natural in the course of old age. Temporizing, delay in diagnosis and finally reluctance to suggest surgery are all too common errors on the part of the physician in his attendance on elderly patients. Early diagnosis in cancer of the colon not only offers a chance for cure but avoids the high mortality accompanying intestinal obstruction in the aged. The complaints of the elderly should be heeded and given as serious study and attention as those of younger persons. The operative mortality among the patients with cancer of the gastrointestinal tract in this series, including those who succumbed after emergency surgery

done for acute intestinal obstruction, was 29.5 per cent, and although this figure seems high, it represents a considerable improvement over the reported results of ten years ago. When carcinoma of the gastrointestinal tract in elderly persons can be treated by elective operation the mortality figures are substantially lower.<sup>12</sup>

An outstanding achievement in the surgery of cancer of the gastrointestinal tract has been the

TABLE 4. Mortality in 140 Abdominal Operations Performed on 129 Patients Seventy Years of Age or Over.\*

TYPE OF OPERATION	NO. OF OPERATIONS	DEATHS IN HOSPITAL																																																																																	
Gastric (16 operations, 2 deaths)																																																																																			
Gastrostomy	2	0																																																																																	
Gastrojejunostomy for cancer	1	1	Gastric resection for ulcer	2	1	Gastric resection for cancer	4	1†	Diaphragmatic hernia repair	1	0	Biliary (36 operations, 6 deaths)			Cholecystectomy	16	3	Cholecystectomy and cholecystostomy	14	0	Cholecystectomy with or without cholecystostomy for carcinoma of gall bladder	3	3	Cholecystenterostomy	3	0	Intestinal (53 operations, 19 deaths)			Resection with anastomosis (2 cases of intestinal obstruction)	9	2	Fistulization resection	1	1	Resection of rectum	4	2	Tube resection prolapse of rectum	1	1	Hemicolectomy	10	5	Ceconomy (all ileocecal obstructions)	6	1	Ceconomy (3 cases of intestinal obstruction)	5	0	Closure of colostomy	4	2	Enterostomy (3 cases of intestinal obstruction)	4	2	Ceconomy (25 operations, 1 death)			Isoperic cancer	6	0	Adhesive bands, intestinal obstruction	5	0	Closure after antiseptic	2	1	Pancreatic	1	0	Mitochondria	9	1	Hysterectomy	4	0	Appendectomy (acute appendicitis)	4	0	Totals	140	27
Gastric resection for ulcer	2	1	Gastric resection for cancer	4	1†	Diaphragmatic hernia repair	1	0	Biliary (36 operations, 6 deaths)			Cholecystectomy	16	3	Cholecystectomy and cholecystostomy	14	0	Cholecystectomy with or without cholecystostomy for carcinoma of gall bladder	3	3	Cholecystenterostomy	3	0	Intestinal (53 operations, 19 deaths)			Resection with anastomosis (2 cases of intestinal obstruction)	9	2	Fistulization resection	1	1	Resection of rectum	4	2	Tube resection prolapse of rectum	1	1	Hemicolectomy	10	5	Ceconomy (all ileocecal obstructions)	6	1	Ceconomy (3 cases of intestinal obstruction)	5	0	Closure of colostomy	4	2	Enterostomy (3 cases of intestinal obstruction)	4	2	Ceconomy (25 operations, 1 death)			Isoperic cancer	6	0	Adhesive bands, intestinal obstruction	5	0	Closure after antiseptic	2	1	Pancreatic	1	0	Mitochondria	9	1	Hysterectomy	4	0	Appendectomy (acute appendicitis)	4	0	Totals	140	27			
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\*Carney Hospital series.

†Total gastrectomy.

trans thoracic approach and resection for cancer of the esophagus and cardiac end of the stomach.<sup>13</sup> Cancer of the esophagus is a disease of the older age group. Sweet's<sup>14</sup> recent report of his experiences in performing esophageal resection with high intrathoracic esophagogastric anastomosis reveals that half his patients were sixty-five years of age or more and 5 patients were seventy or over. The results obtained in the surgical treatment of cancer of the esophagus not only are remarkable in themselves but also offer the most convincing evidence supporting a contention that advanced age is not at all an insurmountable obstacle to radical extirpative surgery for cancer.

**Urgent abdominal surgery.** Thirty-one of the 140 abdominal operations were done as emergency procedures. Intestinal obstruction was the diagnosis in three quarters of these patients and accounted for 10 of the 12 deaths in the group. Cutler,<sup>15</sup> in

his study on surgery among aged patients at the Goldwater Memorial Hospital in New York City, has reported a similar experience in patients requiring urgent surgery. That old people do not tolerate intestinal obstruction for many hours and that surgical intervention is accompanied by high mortality is the unfortunate experience of all those reporting on this subject.<sup>20</sup> Incarcerated or strangulated inguinal hernia was the cause of obstruction in more than a quarter of the patients with intestinal obstruction, and this fact alone should justify hernia repair by election in those patients whose histories indicate that incarceration has occurred in the past. Quigley<sup>21</sup> has shown that herniorrhaphy is a safe procedure in the aged patient,

TABLE 5 *Mortality in 65 Abdominal Operations Performed at a Time of Election on 57 Patients Seventy Years of Age or Over\**

TYPE OF OPERATION	NO. OF OPERATIONS	DEATHS IN HOSPITAL
Gastric (16 operations 3 deaths)		
Gastrostomy	4	1
Gastrojejunostomy for benign ulcer	2	0
Gastrojejunostomy for cancer	2	1
Gastric resection for benign ulcer	1	0
Gastric resection for neoplasms†	7	1
Biliary (13 operations 1 death)		
Cholecystectomy	5	0
Cholecystectomy and choledochostomy	8	1
Colon (28 operations 5 deaths)		
Resection with anastomosis for cancer	3	0
Exteriorization resection for cancer	6	1
Resection of the rectum for cancer	8	2
Ileocolostomy for cancer	1	0
Colostomy for diverticulitis	3	0
Colostomy for nonresectable cancer	4	1
Closure of colostomy	3	1
Celiotomy with exploration (nonresectable cancer)	8	0
Totals	65	9

\*Excluding urgent surgery (Welch's personal series)

†For cancer in 5 and for adenoma of the stomach in 2 cases

incurring small risk. Femoral hernia in the elderly female is very frequently unrecognized both by the patient and by the physician. A careful examination for small masses protruding from the femoral ring is a most important part of physical diagnosis in elderly women with obvious obstruction of the small intestine. Fortunately, strangulation of the bowel is infrequent with femoral hernia.<sup>22</sup> Acute appendicitis is rather rare among the aged, and, in our series, there were only 4 patients with this disease among 542. It is important to bear in mind that symptoms of appendicitis in the aged are insidious and that the disease is frequently advanced a few hours after the onset of pain. The majority of elderly patients are found to have gangrenous appendicitis or perforation at operation. Early operation is essential.<sup>23</sup> Perforation of a peptic ulcer is sometimes encountered even in the very old, and this disaster is often fatal.<sup>24</sup> In general, it is true that peritonitis is poorly tolerated in these patients. The treatment

of massive hemorrhage from gastric and duodenal ulcer is an equally important aspect of the peptic-ulcer problem in older persons. Since the publication of Allen and Benedict<sup>25</sup> in 1933 a great deal has been written to emphasize the fact that a higher mortality attends ulcer hemorrhage as age progresses.<sup>26</sup> Surgical intervention has been suggested and carried out sporadically.<sup>27, 28</sup> The relative merits of nonoperative and operative treatment for the very old patient have not been decided. Although surgery may prove to have a useful field in the immediate treatment of hemorrhage in some patients beyond the age of fifty, it is doubtful that operative intervention is the wise course in the very old since an extensive gastric resection is usually required for the control of bleeding involving high risk under these conditions. Co-operation between the physician and surgeon in the management of these patients, however, is most desirable, and recent advances in our present appreciation of the significance of blood loss and blood replacement in the management of patients with hemorrhage from ulcer has offered a better prognosis by nonoperative management than that obtained under the conditions of the older policy of starvation and dehydration.<sup>29</sup>

**Biliary surgery** Surgery of the biliary tract accounted for about a quarter of the abdominal operations in the Carney Hospital series (Table 4). The significant feature of biliary-tract surgery in the aged is that over half the patients are found to have complicated disease—common-duct stone, acute cholecystitis or cancer of the gall bladder. Often elderly patients have obstructive jaundice and in some cases jaundice has been allowed to exist for long periods of time. Quigley<sup>30</sup> has reported a mortality of 13 per cent for biliary surgery in patients aged sixty-five or over with gallstones and has clearly pointed out the increased morbidity and mortality that accompany surgery for this disease in the aged group as related to the complicating factors of acute cholecystitis and obstructive jaundice. The mortality for simple cholecystectomy done as an elective procedure is relatively low even in patients of advanced age. Glenn and Heuer<sup>31</sup> have stressed the importance of performing surgery of the biliary tract in the early decades of life to avoid the high mortality associated with emergency procedures for acute cholecystitis as age increases. The problem of advising surgery in patients with gallstones seems always to present a dilemma for the physician. It is difficult to make hard and fast rules but the facts about gallstones in the aged patient should be borne in mind at the time of decision in younger subjects with cholelithic disease.

**Elective abdominal surgery** When adequate preparation before operation is possible, there is, of course, greater safety for the patient, and morbidity is correspondingly less. In a separate con-

secutive series of 57 patients aged 70 years or more, upon whom we performed 65 abdominal operations electing the time and conditions for surgery, the mortality was found to be 15.6 per cent for patients and 13.8 per cent for operations (Table 5). These operations were done largely before the extensive use of chemotherapy and antibiotics. Surgery of the biliary tract carried the least risk. Operations on the stomach, colon and rectum were accompanied by approximately three times the risk of that for operations on the gall bladder and bile ducts for gallstones. Cancer of the stomach, with its known tendency to early metastasis and extension, probably offers the most serious operative surgical problem in the elderly patient if cancer of the pancreas and bile ducts is excluded. The operations of total gastrectomy, transthoracic esophagogastrectomy and partial gastrectomy done as a palliative procedure are understandably attended by higher mortality rates than extirpative operations for cancer of the colon and rectum. The nature and extent of the disease again seems to be the common denominator influencing the outcome for the patient.

### *Urologic Surgery*

The necessity of relieving urinary obstruction in the elderly male patient is the principal problem in urologic surgery. In addition to the treatment of benign prostatic hypertrophy, cancer of the prostate assumes greater importance as age progresses.<sup>22</sup> It is also true that a higher mortality rate may be expected in surgery for cancer of the prostate. Recently, castration and estrogen therapy have come to have a significant role in the disease and offer additional benefits for the old patient.<sup>23-25</sup> In general, progress in urologic practice has had a great deal to offer the elderly male patient. It is interesting to note that the urologic service at the Carney Hospital performed the largest number of operations although the number of patients upon whom the urologists operated was slightly less than that of the abdominal-surgery group. The total operative mortality was 9.4 per cent for 149 operations and 12.4 per cent among 113 patients. Many of these patients entered with acute urinary retention, and, indeed, some of the deaths occurred in those who succumbed after suprapubic cystostomy alone. It has been well established that prostatectomy can be done with reasonable safety today by any of the several techniques, and enormous improvements have been made in the preoperative, operative and postoperative care of patients with urinary-tract obstruction.

Before a period of ten years ago the mortality from the operation of prostatectomy throughout this country was in the neighborhood of 15 or 20 per cent, according to Cabot,<sup>26</sup> for patients of all ages. At the present time the mortality rates for the suprapubic, perineal or transurethral methods

of resection are probably in the neighborhood of 4 per cent or less,<sup>27, 28</sup> depending upon the selection of patients submitted to these procedures.

Without entering too far into the somewhat controversial field of prostatectomy technique, on which I am not qualified to speak, a survey of the literature indicates that two things have been especially valuable to urologists in including a larger number of elderly patients in the group for prostatectomy. The first of these is the marvelous safety of low spinal anesthesia in these operations. Small amounts of drug only need be given, anesthesia is of short duration, and recovery rapid. The second factor is the more universal use of the transurethral method of prostate resection in patients of uncertain risk who, fifteen or twenty years ago, might otherwise have been consigned to a catheter life or to permanent suprapubic cystostomy.<sup>29, 30</sup>

### *Ophthalmologic Surgery*

Surgery of the eye has been done on aged patients for many years, and perhaps the ophthalmologists should be considered pioneers in geriatric surgery. Ophthalmologic surgery was possible at an earlier date than other operative work because the hazard to life has been negligible in this field. There were 2 deaths among 67 patients operated on at the Carney Hospital, but neither was related to the surgical procedure and might have occurred in these patients at any time. Operations for cataract are highly successful,<sup>31</sup> and the surgical treatment of glaucoma has offered immeasurable comfort to many of these patients. Not only has eye surgery been a boon to the aged patient but also the alleviation of blindness very often relieves the family by converting a burdensome elderly person into a useful member of the household. In the Carney Hospital series, eye surgery ranked third in importance among aged patients.

### *Surgery for Peripheral Vascular Disease*

Fifty-four of the 542 patients in our group required operation for problems related to disease of the blood vessels of the lower extremities. About half these patients were treated for varicose veins or for thrombophlebitis by the various established ligation procedures. Prophylactic ligation of the deep leg veins for the prevention of thrombosis and embolism was not generally practiced. Ligation after evidence of deep phlebitis, however, was done in a number of patients.

Arteriosclerotic gangrene of the leg, sometimes complicated by diabetes, made up the most serious problem. Twenty-six patients required amputation of some portion of the extremity, and 23 of these underwent thigh amputation. Six patients (21.6 per cent) died after thigh amputation. This mortality rate represents a reduction from that which could have been achieved fifteen years ago in patients of this age. In addition to the many

new supportive measures that are applicable to all surgical patients, the control of sepsis by chemotherapy and antibiotics deserves special mention in the better results now obtained in patients with gangrene of the leg. The use of refrigeration before surgery and of refrigeration anesthesia as reported by O'Neil<sup>42</sup> and others<sup>43</sup> seems to have been a definite implement in reducing mortality in the hands of some surgeons. In the management of gangrene of the leg at the Carney Hospital, refrigeration anesthesia was not used extensively, but the control of infection and the adequate use of blood transfusions were found to be most important before and after operation. Low spinal anesthesia was employed almost exclusively. McKittrick<sup>44</sup> has shown that the use of penicillin and control of sepsis have made possible conservative transmetatarsal amputations in diabetic patients, some of whom, in former years, would have been subjected to major amputations. The outlook for patients with gangrene of the leg has immeasurably improved in the last few years.

### *Orthopedic Surgery*

We can all recall the disheartening picture presented by the large number of old men and women with fractured hips who crowded the surgical wards up until recent times, and although the problem of the fractured hip is still a very difficult one and far from solved, fewer patients die in the early period after fracture and many are quickly made ambulatory. Before the beginning of the extensive use of internal-fixation procedures, many of these patients with hip fracture rapidly succumbed from bronchopneumonia. Others developed huge decubitus ulcerations, which made them a great nursing problem and hindered their chance of recovery. At best, unsatisfactory treatment with indifferent results after a long hospital stay was the lot of those who survived. At the present time, the work of the orthopedic surgeon in the early operative treatment of femoral-neck and intertrochanteric fracture has greatly lowered the mortality, decreased morbidity and reduced the patient's hospital stay.<sup>45-48</sup> Low spinal anesthesia has proved to be the best choice for these procedures. Ideally, patients of advanced age, even those over eighty years of age, are operated upon within forty-eight hours of injury and rapidly made ambulant. The reduction in the incidence of decubitus ulceration has been one of the most important aspects of this program. It is true that the incidence of nonunion is high in the aged, but this fact does not influence the immediate value of the results now obtained. In the Carney Hospital series the average age of 37 patients undergoing bone and joint surgery was seventy-seven years, and fracture of the hip was the principal problem (Table 1).

Approximately a third (33.6 per cent) of the deaths in patients seventy years of age or over in Massachusetts during 1946 were accidental in nature, and accidents rank fourth in both sexes as a cause of death in elderly people. Prevention of home injuries might be a useful interest of the general practitioner as he visits his elderly patients, since hip fracture usually occurs in the home and its prevention is still worth more than all that our accomplishments have added to the treatment of this injury.

### *Gynecologic Surgery*

As age advances, the need for the gynecologist's services diminishes. Only 7.6 per cent of the operations in the Carney Hospital group of elderly patients were done for diseases of the female genital tract. Forty operations were performed, and 14 of these were carried out from below. Cancer in this group of patients, however, requires major operation, and the distressing condition of uterine prolapse is a major affliction for some elderly women. Fortunately, operations by the perineal route are well tolerated and accompanied by a low mortality.<sup>49</sup> There should be little hesitation in recommending surgery for herniation of the bladder or for other lesions resulting from relaxation of the pelvic floor in women of advanced age.<sup>50</sup>

### *Other Important Operative Procedures*

In the groups of operations classified as miscellaneous in Table 1 thyroidectomy for hyperthyroidism and dissections of cervical lymph nodes in the treatment of metastatic cancer require mention. Lahey<sup>51</sup> has called attention to the manifestations of hyperthyroidism in older patients.

Relief of pain by neurosurgical procedures has a larger field than might be indicated by the absence of these operations among the elderly patients in our series. The operation of prefrontal lobotomy, now under trial, may become especially useful in the aged group. Tic doloieux is not infrequently encountered in the aged, and the relief of persistent pain after herpes zoster, peculiar to these patients, also presents a need for operative neurosurgery. Operations for the removal of brain tumors in patients over seventy are seldom carried out, but with the risk of intracranial surgery becoming less, we may expect that neurosurgeons will recommend operation among this group more frequently in the future. A great deal will depend upon the status of the patient and his disease, but increased risks in this field might be justified if a few useful members of society can be made out of persons who otherwise look forward to a vegetative existence.

### ANESTHESIA

The passing of the epoch when anesthesia was by necessity performed as a side issue to surgery by the youngest hospital staff member as he began

his hospital training, or later as he launched into practice, marked a great advance in modern surgery. Progress in anesthesia required the recruitment of physicians whose interests were not divided. The firm establishment that this specialty now enjoys with its separate training program and attractive opportunities for its qualified men is sure to keep offering continued advantages for the patient. The increased requirements that surgeons have made on the anesthetist's skill and knowledge as they have extended extirpative surgery for cancer and invaded new areas continue to be a great stimulus to these new specialists.

There is considerable discursive literature on the subject of selection of anesthesia for the elderly patient.<sup>22, 23</sup> All the evidence seems to show that in the hands of expert anesthetists there is a place for almost all technics and agents if an individualization of the patient's requirements is carefully made. From the standpoint of the poor-risk patient, several tangible facts about anesthesia seem to stand out that might permit of generalization. The first of these is obvious — an experienced anesthetist is the first requisite for difficult surgery, not only is he needed in the selection and administration of the anesthetic but also he removes a great load of responsibility from the surgeon's shoulders in assuming the management of blood and fluid replacement during the course of the operation. During the early postoperative period he has much to offer in preventing and treating pulmonary complications.

Regarding the selection of anesthetic agents and technics for elderly patients, agreement exists among the majority of anesthetists to a reasonable degree although there cannot be said to be a unanimity of opinion about the generalization I shall make.

Regional nerve block and local infiltration have a field of usefulness but the extent to which these procedures can be put is limited by the operation required and by the experience of the administrator. Certain nerve-blocking procedures require great experience and practice for satisfactory execution, and very few anesthetists have mastered all of them. Low spinal anesthesia is agreed to be ideal for prostatic surgery, for gynecologic surgery performed from below and for amputations of the leg. The paralysis produced fortunately involves only a limited amount of the autonomic and somatic nervous system.<sup>24, 25</sup> High spinal anesthesia involving nerve paralysis of a larger part of both systems is attended by greater fluctuations in the blood pressure and often by depression of respirations. Cardiovascular changes are almost always present in elderly persons, and under these circumstances high spinal anesthesia is not the best choice. Inhalation anesthesia using cyclopropane or ether and the endotracheal tube has proved most satisfactory and safe for

old patients undergoing surgery of the upper abdomen in the opinion of many anesthetists. Intravenous anesthesia using pentothal sodium not only has its limitations of usefulness as a single agent, often requiring combination with others, but also, because of its depressant and toxic action in large doses, cannot be considered safe for the elderly patient.

The least strain that is put upon the patient during the whole surgical procedure, including the induction of anesthesia, the better for the elderly patient, whose limits of physiologic adjustment are confined to narrower ranges than those of younger persons. Reasonable speed without dangerous haste in the accomplishment of an operation likewise may lessen the burden on these patients since a long operating time has been found to be a factor influencing mortality.<sup>26</sup>

#### SURGICAL ADJUNCTS AND SAFEGUARDS

Bringing the elderly patients safely through major surgery has no specific formula. All measures found useful in the safe conduct of the adult surgical patient apply to the elderly, but must be intensified in their application. Wangensteen<sup>27</sup> points out that greater precision in the application of all measures in the preoperative period at operation and during the postoperative course is mandatory in the management for the very old patient who is a border-line risk. He rightly cautions us to avoid that allowance of latitude in our exactness which in the younger person does not turn the balance unfavorably. True also is his statement that seldom does the old patient suffer from one disease. The principal cause of death in old age is heart disease, and cardiac deaths and peripheral-vessel accidents account for more than half the fatalities in patients over the age of seventy. The aged patient comes to surgery with handicaps that cannot be greatly improved in the preoperative period, but must be heeded in the estimation of risk and in the management of the entire surgical performance. Cannon<sup>28</sup> has summarized the aged person's capacity in the following statement:

A survey of the chief agencies concerned in maintaining homeostasis of the acid base balance — lungs, blood vessels and heart — shows that as life proceeds to its later stages there is likely to be in each of these organs a narrowing of the capacity to adjust for special requirements. A routine existence within the limits of easy adaptation may continue indefinitely without revealing any weakness, but exposure to a stress which encroaches on the limits quickly discloses that they have become much restricted.

In the changing scene of surgery today we may point to certain stabilized adjuncts that have greatly influenced our good results and increased the width of the application of surgery to the aged. Of all these benefits, which have come in many forms such as chemotherapy in the preparation of the intestinal tract for operation, antibiotics

and chemotherapy in the treatment of infection and new anesthetic drugs and technics, none can compare, I believe, with the help that a safe procedure for blood transfusion has provided. The universal use to which this supportive measure has been put by the surgeon in the correction of severe anemia and the restoration of blood volume before surgery, as well as in the replacement of blood as it is shed during operation, has perhaps no peer in supporting surgical practice. The newer studies of Lyons<sup>59</sup> have shown us particularly the importance of blood-volume estimations as an index for estimating the blood-replacement needs in patients if they are to be optimally prepared to withstand long and difficult surgical procedures. Elderly patients with cancer of the gastrointestinal tract exhibiting weight loss have a reduced blood volume, and under these conditions are more vulnerable to surgical shock at operation and less well prepared to meet the postoperative period. Indications for adequate preoperative transfusion therapy require blood-volume studies, since accurate information from the blood-cell count, hemoglobin value, hematocrit reading and plasma protein determinations are misleading and do not estimate this factor of the quantity of available circulating mass. Wangenstein's<sup>60</sup> practice of accurately measuring blood loss during operation with quantitative replacement represents a particular refinement of supportive treatment by blood transfusion. Clinical estimations have proved satisfactory in the hands of most groups.

The nutritional deficiencies of elderly patients with cancer of the gastrointestinal tract have been elaborately studied by Varco.<sup>61</sup> Experimental and clinical investigation has related hypoproteinemia and vitamin deficiency to poor tissue healing.<sup>62-65</sup> The application of the knowledge to practice probably has not kept pace with these developments. The dietary management of patients who have sustained great loss of weight during their disease has been carefully described by Wangenstein<sup>60</sup> and by Varco,<sup>61</sup> but few of us have had the patience to carry out these details. Rapid preparation of depleted patients by adequate blood transfusion is the common practice, and may be the better choice under most circumstances since preparation time is not unlimited.

Adequate hydration is necessary, but too often in the elderly person overhydration is practiced. Excessive sodium administration can, in the presence of a weak heart, actually precipitate failure that may be fatal and probably represents an insufficiently appreciated cause of death in the postoperative period.<sup>66</sup> It is not a bad practice to run the elderly patient a little short on sodium chloride.

One of the most difficult situations in the elderly patient is that of pressure necrosis of the skin, with its resulting bedsores.<sup>66</sup> Its treatment is difficult, and its prevention our best hope. Constant mov-

ing of the patient as soon as he becomes confined to bed, with the alleviation of pressure on the areas that usually bear weight in the dorsal decubitus position, is the best insurance against this complication.

I have mentioned prophylaxis directed at decreasing the incidence of thrombophlebitis and pulmonary embolism by ligation of the deep veins of the leg now widely practiced since the demonstration by Homans<sup>67</sup> of its value in the prevention of embolism. Allen and his associates<sup>68, 69</sup> at the Massachusetts General Hospital are convinced of the efficacy of this practice carried out under the conditions of their routine and report a reduction in the incidence of fatal embolism among their patients. Good results in the control of this complication have also been reported by those who have used anticoagulants, in the form of either dicumarol<sup>70, 71</sup> or heparin.<sup>72, 73</sup> The majority of surgeons today, however, pursue what would seem to be a middle course program tending to rely on early ambulation and exercise as a preventive measure, and daily examination of the legs for detection of thrombophlebitis in the deep veins. Anticoagulant therapy and vein ligations are then reserved for treatment. That the answer to this problem remains to be solved, all will agree.<sup>74</sup> In the elderly patient, the known higher incidence of fatal embolism, however, makes it mandatory that some program be adopted, for loss of life from embolism has come to be considered in many quarters a surgical error.

Last of all, but not least, the long-term training programs in surgery conducted in our teaching hospitals offer an experienced full-time resident staff immediately available for the necessary vigilant care of patients whose survival may depend on special knowledge promptly applied at a critical time. In addition, each year for many years met have been moving out from these centers to community practice where they are on the scene to answer the surgical needs of our population. If no other country has surgery been taught so extensively by its preceptors, and decentralization of this specialty has moved ahead rapidly, making surgery of a high order available to a larger number of people.

#### SUMMARY

Five per cent of the population of the Commonwealth of Massachusetts is composed of men and women who have reached or passed the age of seventy years. Operative surgery in patients beyond the age of seventy has been demonstrated in the experience of recent years to be relatively safe. The yearly increase in the elderly population in this country indicates that we may expect a larger requirement for surgery among the aged as time goes on. The recognized higher surgical mortality rates in these patients are constantly decreasing.

and, at the same time, more extensive and formidable procedures are being successfully applied. Diseases of the heart and blood vessels represent the principal causes of death among patients who succumb during the postoperative period for reasons not directly related to the operative work. Our efforts must be directed toward making surgery even safer for these patients by concentrating on increasing our accuracy in the application of the details of surgical care so that mortality rates reach the irreducible minimum possible with present knowledge.

As physicians, entering a period in which the problems in geriatrics are on the increase, we owe a responsibility to our aged patients to approach the investigation of their illnesses with the same perspective that we do in the case of younger persons — that is, with the conviction that the outlook is not hopeless in many cases if surgery is needed. The high mortality rates among the elderly who must undergo surgery as an emergency can be avoided by earlier diagnosis and planned surgery at a safer time in a substantial number of cases. Early diagnosis and prompt acceptance of surgery in old patients with cancer seem to offer a particularly fruitful field for improvement.

In the preparation of this manuscript, I have received the helpful advice of many of my colleagues in the Department of Surgery. Particularly I wish to express my indebtedness to the members of the Carney Hospital Surgical Staff and to Dr. Herbert L. Lombard, director of the Division of Cancer and Other Chronic Diseases, Massachusetts Department of Public Health.

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was diagnosed with plain films in 2 patients, and bronchography was therefore not done. There were no characteristic bronchographic findings to suggest foreign-body aspiration.

### Bacteriology

Bacteriologic examination of the sputum was done in only 5 patients. Alpha and gamma streptococci, *Staphylococcus aureus*, and *Haemophilus influenzae* were reported. The isolation of *H. influenzae* from the sputum of 1 patient led to a diagnosis of in-

### Operations

Lobectomies were performed in 7 cases, the right lower lobe being removed in 6 cases and the left lower lobe in 1. Hilar-dissection technic was used in all but 1 case. Dense pleural and diaphragmatic adhesions were encountered in 6 patients.

The postoperative course was uneventful in 6 cases. One patient with unusually extensive intrapleural adhesions and a long operation showed a low daily rise in temperature until the seventeenth postoperative day. There was incomplete pulmonary expansion and intrapleural fluid on the side of operation during this period. No wound complications were encountered. All patients were asymptomatic at the time of discharge.

### Follow-up Study

Follow-up information is available on all patients, the observation periods varying from two months to four years. The 7 patients who have had lobectomies are well. The one who had bronchoscopic removal of the timothy head without lobectomy has been well for four years.

### PATHOLOGY

The excised lobes showed similar pathologic changes, which varied only in degree. There were no specific changes that could be attributed exclusively to the action of timothy grass. Three of the lobes contained basilar abscesses, and in 2 of these the timothy was found by the pathologist. In the third, the timothy was removed at operation by rupture of the peripherally placed abscess while the pleural space was being dissected. The lobes in 4 cases showed classic bronchiectasis, as in Case 6 (Fig. 2), with irregularly dilated bronchi measuring up to 1 cm in diameter. The bronchial walls were thickened up to 0.6 cm. Timothy heads were found lying within ectatic bronchi in 2 cases. The timothy heads were always found stem downward, with their barbules pointing upward.

All lobes after removal were formalin fixed. Multiple tissue blocks were then obtained from characteristic areas, and sections were stained with hematoxylin and eosin, either Mallory's or Masson's connective-tissue method and Verhoeff's elastic-tissue stain.

The most striking histologic finding was extensive connective-tissue proliferation about the bronchi and vessels with extension along all the pulmonary septums. This was most marked in patients who had prolonged illness and was least obvious in those from whom the foreign body was removed bronchoscopically. Six cases showed a cellular intra-bronchial exudate. In 5 of these there was marked organization, with conversion of the exudate to active granulation tissue. The response of the bronchial mucosa varied from slight proliferation of columnar epithelial cells to production of thick

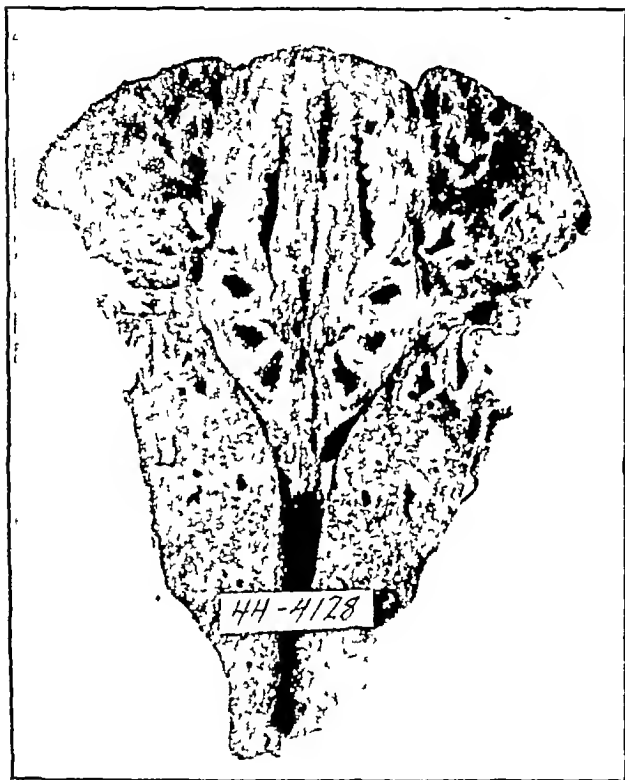


FIGURE 2 Hemisected Right Lower Lobe in Case 6, Showing Extensive Bronchiectasis

fluenzal pneumonia, and aerosol streptomycin was given without effect. No bacteriologic pattern characteristic of timothy aspiration was observed, although no special mediums were used.

### Duration of Foreign-Body Stay

The duration of stay of timothy in the bronchi varied from two to thirty-six months. In patients under the age of three the average stay was three months. In patients over six years of age the average stay was nineteen and a half months. In the 7 patients requiring surgery the period from the onset of symptoms to lobectomy varied from four months to three years.

squamous epithelium. Diffuse peribronchial infiltration with lymphocytes and large lymph-follicle formation in the submucosa were prominent in all cases. The elastic and smooth-muscle layers of the bronchi were disrupted and replaced by connective tissue and chronic inflammatory cells. Eosinophils, plasma cells and lymphocytes were the most common inflammatory cells in all lobes, but polymorphonuclear leukocytes were numerous immediately surrounding the abscesses. A marked intimal obliterative endarteritis was present in 4 cases, Fig. 3 shows the histologic findings in Case 7. This was most extensive near the diseased bronchus or abscess cavities. A large thrombosed and partially recanalized vein was found communicating with an abscess cavity in one lobe.

The alveoli of all excised lobes contained varying amounts of edema fluid, red cells, chronic inflammatory cells and macrophages. Some macrophages were fat laden, whereas others contained pigment. Multinucleated giant cells were occasionally present. The alveolar walls were variably thickened. In some areas alveoli were isolated by proliferating

months in the bronchi of the latter group. In addition, the timothy heads were more peripherally located in the lungs of the older patients.

Unstained smears were made of scrapings from the bronchial walls adjacent to the timothy head



FIGURE 4. Unstained Smear from the Bronchial Wall in Case 5, Showing Timothy Barboles (x63).

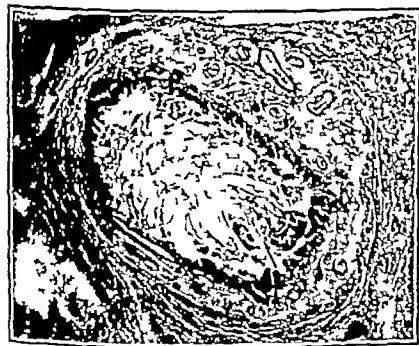


FIGURE 3. Cross Section of Timothy in the Bronchus in Case 7 with Masson's Trichrome Green Stain (x6). Note the marked obliterative endarteritis of the bronchial vessels and the thickening of the bronchial wall.

in 2 cases. Spicules of fibrous vegetable material were easily seen in both (Fig. 4).

#### CASE REPORTS

The following case histories are considered typical. In Case 3 the foreign body was removed bronchoscopically, but bronchiectasis had become established, so that lobectomy was ultimately necessary for cure. In Case 6 the foreign body remained undiagnosed for a long period and caused marked debility before lobectomy was performed.

**CASE 3.** C. F., a 2 2/12 year-old boy entered the hospital with a history of cough and intermittent fever after "swallowing" a piece of grass at the age of 17 months. A diagnosis of pneumonia was made, and chemotherapy given. The child was then taken out of the hospital against advice, but because of a continued septic course hospital care was sought again after an interval of 2 1/2 months. On this admission a foreign body was suspected, and at the first bronchoscopy a timothy tip was recovered from the right lower lobe bronchus. The patient subsequently improved clinically, but repeated bronchograms over the next 9-month period showed extensive and progressive bronchiectasis of this lobe. For this reason lobectomy was performed. Pathological examination revealed no additional foreign material. He has been asymptomatic for 1 year and no pulmonary complications have developed.

**CASE 6.** S. S., a 7 11/12 year-old girl gave the history of a choking spell at the age of 5 years after chewing grass in the early summer. One week after this episode she was hospitalized with a diagnosis of pneumonia. The infection did not respond to chemotherapy and empyema resulted. Three thoracotomies and later three rib resections were done. The patient was chronically ill and out of school for 1 year. Three years after aspiration she had a chronic cough, foul

connective tissue and were lined with darkly staining cuboidal epithelium.

In general, the diffuse acute inflammatory response was most marked in patients under three years of age. Localized abscess formation, diffuse chronic inflammation, fibrosis and obliterative endarteritis were all most marked in children over the age of six. However, the average sojourn of the foreign body in the bronchi of the former group was three months compared to nineteen and a half

sputum and x-ray evidence of bronchiectasis of the right lower lobe. The timothy was found in a subpleural abscess at operation, and lobectomy resulted in a cure.

### DISCUSSION

The Jacksons<sup>1</sup> have pointed out many reasons why the diagnosis of inspired foreign bodies is so often missed. Failure to elicit the history and failure to consider the possibility early in the course of the illness were the two principal reasons for misdiagnosis in the 8 patients described above. They illustrate the prolonged and disabling illness that may result when the correct diagnosis is not established. A foreign body was ultimately considered in all cases, but in only 1 was the timothy removed early enough to effect a cure without lobectomy.

The symptomatology is characteristic only of pulmonary infection unless a major bronchus is completely obstructed. In this event immediate massive atelectasis occurs with such severe symptoms that more aggressive efforts are usually made toward diagnosis. In this small series the correct diagnosis was established earlier in patients under the age of three. It is logical to assume that the smaller bronchi of very young children lodge the timothy at a higher point. Thus, the youngest patient in the series was bronchoscoped because of atelectasis following aspiration, and the timothy was removed. This was the only case in which lobectomy was not required.

In all 8 patients, as well as in those reported in the literature, the grass heads were oriented stem downward so that movement was possible in a peripheral direction only. In the older children with larger bronchi the grass progresses distally and is soon lost from bronchoscopic view. In this group localized abscess formation with empyema and pyopneumothorax is more common because of the subpleural position of the foreign body.

Severe hemoptysis in a child should immediately suggest the possibility of a foreign body. In 1 of the patients reported by Butler et al.<sup>5</sup> timothy fibers were found in blood coughed from the lungs. Timothy fibers were also found in smears made from the bronchi of the excised lobes in 2 cases of this series. These findings suggest the value of un-

stained smears of blood or bronchial secretions in the diagnosis of inspired vegetable foreign bodies.

The locality in which the patient lives and the season of the year are further clues to be considered. One would expect grasses or grains to be inspired during their flowering seasons. This season for timothy is during June and July in this locality.

The uniform operative procedures and the uneventful convalescence of these 7 patients illustrate the low risk of lobectomy in young patients. Even though the presence of a foreign body cannot be established, recurrent hemoptysis from an obviously damaged lobe or known bronchiectasis should be an indication for surgical treatment when tuberculosis has been excluded.

Two additional cases of Timothy grass aspiration have come to our attention since the completion of this study. In one of these bronchoscopic removal was possible.

### SUMMARY

Eight cases of timothy-grass foreign bodies in the bronchi are presented. Seven of these required lobectomy because of subsequent bronchiectasis or lung abscess.

The peculiarities of this foreign body are discussed.

No specific pathologic lesion was found in the cases presented.

Suggestions for early diagnosis are made.

We are indebted to the following for the use of their case histories: Drs. Ralph Adams, Robert E. Gross, Thomas H. Lanman, Richard H. Overholt, John W. Strieder, Richard H. Sweet, and Orvar Swenson, all of Boston, and to Dr. George E. Cummings, of Portland, Maine.

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## COEXISTING PULMONARY COCCIDIOIDOMYCOSIS AND TUBERCULOSIS\*

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## CASE REPORT

PRIOR to World War II, coccidioidomycosis was a relatively rare disease known chiefly to physicians in the San Joaquin Valley and a few other scattered areas in the southwestern portion of the United States. Winn,<sup>1</sup> in 1941, reported a series of 12 cases in which attention was called to the frequency of pulmonary cavitation as a manifestation of coccidioidomycosis.

During the war, when hundreds of thousands of troops were assigned for desert maneuvers in endemic areas such as Arizona, southern California and southwestern Texas, a large number acquired coccidioidal infection with pulmonary cavitation. As a result, many medical officers were brought into personal contact with the problem of differentiating the pulmonary lesions of coccidioidomycosis and those of tuberculosis. Several comprehensive articles have recently appeared in the literature dealing with all phases of the disease, including its roentgenologic differentiation from tuberculosis.<sup>2-4</sup>

Although there is no reason that tuberculosis and coccidioidomycosis cannot coexist, the literature contains only three such reports.<sup>4-6</sup> However, Dr C. E. Smith,<sup>7</sup> of Stanford University, indicated that he had seen a number of cases in which coccidioidal infection was superimposed on active pulmonary tuberculosis and 2 with tuberculosis superimposed on coccidioidal cavitation or active infection. Recently we observed a case in which caseous pneumonic tuberculosis with cavitation developed in a patient who already had a coccidioidal cavity in the opposite lung. Had we not known the previous medical history (at the time of the last admission), the finding of tubercle bacilli in the sputum together with the x-ray picture would have led to a diagnosis of bilateral cavitary tuberculosis, and the coccidioidomycosis would have been overlooked.

This case raises the question whether it would not be wise to do routine examinations for both coccidioides immitis and tubercle bacilli in all cases of pulmonary disease with cavitation. This is in line with the conclusions of Greer and Gemoets<sup>8</sup> that coexisting tuberculosis and fungous infection should be more frequently considered. In a series of about 300 cases of tuberculosis they found parasitic fungi in the tracheal washings in 4 per cent.

I F., a 24-year-old Negro was admitted to the hospital in December 1945. Pulmonary tuberculosis had been diagnosed on routine x-ray examination at a separation center that showed infiltration in both apices and in the right third anterior interspace.

During the war the patient had taken part in desert maneuvers in southern California from June to December, 1943, but had had no respiratory illnesses. The past medical history was noncontributory. The family history was negative for tuberculosis.

On admission the only complaint was intermittent, slight pain in the left side of the chest for the past few months. Physical examination revealed a well developed man who



FIGURE 1. Chest Film Taken on December 6, 1945, Showing Minimal Infiltration in Both Apices and an Area of Irregularly Annular Density in the Right Apex.

did not appear ill. There was no dyspnea or cyanosis and examination of the heart and lungs was negative. There were two healed scars over the left ankle and foot from an old gunshot wound.

A x-ray examination showed minimal infiltration in both apices (Fig. 1). Because of an area of irregularly annular density above the right clavicle, planigrams were taken on January 19, 1946, confirming the presence of a small thin-walled cavity (Fig. 2).

Significant laboratory findings at that time were as follows. A tuberculin skin test using purified protein derivative was negative in the first strength and weakly positive in the second strength. Coccidioidin skin test in a 1:1000 dilution was negative on two occasions. Sputum concentrates examination of the gastric contents, one sputum culture and one guinea pig inoculation were negative for tubercle bacilli. One 72 hour concentrate was negative for fungi. The sedimentation rate was 8 mm in 1 hour. Urinalysis showed a trace of albumin. Blood counts were within normal limits.

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The patient left the hospital against advice in March, and the discharge diagnosis was chronic pulmonary tuberculosis, moderately advanced.

The patient returned to the hospital on June 13, with the chief complaint of bilateral chest pain and a slightly productive cough.

Physical examination and x-ray films of the chest showed no essential change since the previous admission. There was the same isolated, thin-walled cavity in the right apex and a small area of infiltration in the left apex.

A coccidioidin skin test was positive on July 2 in a 1:1000 dilution and positive on July 5 in a 1:100 dilution. Sputum studies for acid-fast bacilli, including seven direct smears, five concentrates and three gastric lavages, were negative. On July 15 the sputum was found to contain spherules of *Coccidioides immitis* on direct smear, and this was confirmed by culture on July 20. Serologic tests for active coccidioidomycosis were performed on August 31 by Dr. C. E. Smith, of Stanford University. The complement-fixation test was ++++ in 1:2 and 1:4 dilutions. The precipitin tests were all negative. Dr. Smith concluded that the findings indicated a coccidioidal infection.

Two attempts to close the right apical cavity with phrenicectomy were unsuccessful. Chloroquin was tried empirically, with no favorable result.

The sputum continued to be positive for *C. immitis*, but the symptoms of cough and chest pain cleared. Since at that time there was little evidence that the spherule form of

+++ in a dilution of 1:16. The precipitin tests were negative in all dilutions. Dr. Smith interpreted these results as not being high enough to indicate a coccidioidal dissemination. *C. immitis* was again found in the sputum on smear and culture.

The patient was recommended for streptomycin treatment of the exudative tuberculous lesion but left the hospital



FIGURE 2 Planigram Taken on January 19, 1946, Showing a Definite Thin-Walled Cavity in the Right Apex

*Coccidioides* was infectious,<sup>9</sup> the patient was discharged with maximal hospital benefit on February 19, 1947.

He was admitted for the third time on October 7, because of intermittent hemoptysis since March. He had also lost 10 pounds in the past 6 months. Examination of the chest revealed an impaired percussion note over the left apex posteriorly, with decreased breath sounds and post-tussive rales over the upper half of the left side of the chest posteriorly. X-ray examination on October 8 showed considerable enlargement of the thin-walled cavity in the right apex (Fig. 3). In addition, the upper third of the left lung was involved by a dense confluent type of infiltration, with several ill defined areas of radiolucence. The appearance of the lesion in the left lung was that of a fresh exudative tuberculosis. The temperature ranged between 98 and 99.6°F. Sputum examination showed acid-fast bacilli on both smear and culture. A serologic test for coccidioidal infection was repeated at this time by Dr. Smith. The complement-fixation test was ++++ in dilutions of 1:2, 1:4 and 1:8 and



FIGURE 3 Chest Film Taken on December 8, 1947. The thin-walled coccidioidal cavity in the right apex has enlarged. Caseous pneumonic tuberculosis, with cavitation, has developed in the left upper lobe.

against advice on November 1, before this therapy could be instituted.

### SUMMARY

A case is presented in which coccidioidal cavitation was observed for fifteen months in a patient who subsequently developed a caseous cavity tuberculosis in the opposite lung, with a positive sputum test for tubercle bacilli.

That tuberculosis and coccidioidomycosis may both cause pulmonary cavitation is now a well known fact. Also, since the diseases may coexist in the same patient, it is advisable to check routinely for both tubercle bacilli and *Coccidioides immitis* in all patients with pulmonary cavitation.

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## MALARIA RELAPSE

## Report of a Case Thirty-Six Years after Original Infection

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THE problems of malaria control and treatment after the return of personnel from endemic areas have frequently been reported in the recent literature.<sup>1</sup> Not the least of these problems is the matter of relapse. Whereas this usually occurs within the first two or three months, there are reports of initial relapse one and a half to two and a half years after the original attack.<sup>2</sup> Relapses at longer periods have been observed, but these are in persons with recurring relapse, such as Ross's father, who suffered from repeated attacks for nine years after leaving an endemic area.<sup>3</sup>

The following case, in which the initial relapse occurred thirty-six years (or longer) after the original infection, is believed to be of interest.

## CASE REPORT

A 69-year-old Sicilian laborer was admitted to the University Hospitals, Cleveland on February 21, 1938 on the service of Dr J T Wearn. He complained of chills and fever occurring at "4-day intervals" for the preceding 6 weeks and a painful lump in the upper portion of the left side of the abdomen. "Four days before the onset of these chills he had slipped and fallen, striking the left side of the trunk on the street curbing."

The past history was significant in that the patient had been in the Sicilian Merchant Marine from the age of 7 to 33, calling at ports as far as the South Pacific. He had come to the United States in 1902 and had lived in the vicinity of Cleveland ever since. He stated that he had had one attack of malaria in Sicily, but he did not recall his exact age at the time. He denied any recent hypodermic injections.

Physical examination revealed a fairly well developed and poorly nourished, sallow man. He had bilateral lenticular opacities and gingivitis. Aside from occasional extrasystoles examination of the heart was negative, and the lungs were clear. The liver and the spleen could be felt during inspiration; the latter being slightly tender. The remainder of the physical examination was negative.

The temperature was 99.5°F, the pulse 88, and the respirations 20. The blood pressure was 162/88.

Urinalysis was negative. Examination of the blood disclosed a red-cell count of 4,590,000, with a hemoglobin of 90 per cent (Sahli) and a white-cell count of 3800 with 65 per cent neutrophils, 20 per cent small lymphocytes, 2 per cent large lymphocytes and 13 per cent monocytes. The parasites (*Plasmodium malariae*) of quartan malaria were seen within many red blood cells on the day of admission and on the following day.

On the 1st and 4th hospital days the patient had a chill after which the temperature rose to 105 and 104.8°F, respectively. He was given 1 gm of quinine sulfate after the second chill followed by 0.64 gm three times daily. Thereafter he had no further elevation of temperature and was discharged on the 9th hospital day with sufficient quinine to last for 1 week. He was followed in the outpatient department and was last seen at home in July, 1947. He had had no subsequent febrile illness.

## DISCUSSION

It is often difficult, if not impossible, to differentiate malarial relapse and reinfection, since the host

usually continues to reside in an endemic area. In the case reported above reinfection by natural means is highly improbable, and the possibility of previous parenteral medication was excluded.

As in the present case the relapse of malaria may occur at times and in places not likely in themselves to suggest the diagnosis. Diagnosis is further confused by the occasional atypical clinical course.<sup>4</sup> Hence malaria should be considered in any bizarre illness in a person who has either had malaria or resided in an endemic area. That the disease should recur after an interval of at least thirty-six years is admittedly unusual, but serves to emphasize the persistence of latent infection. Such latency, which constitutes a carrier state, illustrates the inadvisability of using as blood donors persons who have had malaria at any time in the past. The patient mentioned by Coggeshall,<sup>5</sup> who transmitted malaria by transfusion thirty-seven years after leaving his native country (Greece), where he had had malaria, further demonstrates this danger.

The cause of relapse in the case reported above is a matter for conjecture. It is now generally considered that during latent periods the plasmodia are undergoing cycles of development within the monocytes and reticuloendothelial cells, the so-called "exoerythrocytic cycle."<sup>6</sup> Trauma, extreme of temperature and fatigue frequently precede relapse.<sup>6</sup> The effect of these external forces is apparently to induce cyclic redevelopment of the parasites in the red cells, with the production of clinical malaria. Such a course may have occurred in this patient after the blow to the area of the spleen.

## SUMMARY

A case of relapse thirty-six years after the original malaria infection is presented.

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## MEDICAL PROGRESS

### PILONIDAL CYST AND SINUS (Concluded)

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#### *Primary Closure*

In this method, after the diseased tissue has been excised, the wound is closed by various types of suturing, in many cases in conjunction with gluteal flap placements, all aimed at effecting successful closure

Ferguson and Mecroy<sup>30</sup> present 37 cases with 92 per cent cures following primary closure under a local anesthetic, an average healing time of seventeen and four-tenths days and two days lost from work

Cohn<sup>31</sup> advocates complete excision with primary closure, using a series of U sutures on either side of the wound edges to include the sacrococcygeal fascia, and finally tying the sutures over a small gauze roll. The patient is kept in the prone position for the entire length of healing

Camp and Polites<sup>32</sup> eliminate dead space by placing the deep and retention sutures beneath the sacrococcygeal ligaments, preventing infection by sifting sulfonamide powder through the closure

Oldham<sup>33</sup> reports 19 cases with 100 per cent success. He creates an elliptical area 12.5 cm or more long, and 7.5 cm or more wide, down to the ligaments of the sacrum and coccyx, and laterally down to the gluteus maximus muscles. He states that primary union can be obtained by aseptic technic, prevention of postoperative infection from the anus, complete hemostasis, obliteration of the cavity left after excision, avoidance of buried absorbable sutures and the use of an eversion suture

Glenn<sup>34</sup> in presenting 120 cases, stresses the postoperative care as follows: the dressings are arranged to seal off the anal region; tension is relieved by strips of adhesive tape extending well over the gluteal region, and a constipating diet, inhibiting the patient's bowels for six or seven days, is adhered to. The position in bed is on the side, with the face slightly downward and the legs straight. The gauze overlying the wound may be kept moist with alcohol, 10 to 15 cc being added every hour for the first six hours. Should the wound become infected, the sutures are removed, and packs soaked with an antiseptic solution such as Dakin's or dichloramine T are inserted

Shute, Smith, Levine and Burch<sup>35</sup> recommended a gluteus maximus flap. A wide double elliptical incision is carried down to the sacrococcygeal fascia,

from which the circumscribed tissue block is separated, a lateral incision down to the gluteal fascia in line of the original incision is then made on either side and deepened into the fibers of the gluteus maximus, and the fibromuscular flap thus created is sutured to its fellow of the opposite side, in the midline. Fifty-nine cases were presented, of which 48 healed primarily in eight days. The remaining 11 developed postoperative infection, healing in twenty-two days

Larsen<sup>36</sup> removes the lesion completely by elliptical block excision, and closes the wound with cotton sutures, employing a meticulous silk technic. Care is taken to place the deepest row of sutures at a level where the deep tissue can be approximated without tension, the sacral fascia is never included in the deep suture layer. Of 225 cases reported primary healing took place in 218, with secondary healing in 7

Pope and Hudson<sup>37</sup> presented 130 cases, with complete healing in all. However, they were unable to check for recurrences. In the 130 cases 92 patients were treated in conjunction with a sliding muscle graft obtained by gluteus maximus cleavage mobilization. The authors claim for this modification closure of all tissues, filling in of the dead space, rapid healing and a protective pad of tissue in the midline

Cattell<sup>38</sup> performs a block excision, with a transplanted gluteal pedicle flap, both ends of which remain attached for a better blood supply. A triangular flap is marked out, with the apex in the lateral gluteal region, on the side opposite the greatest defect made by the block excision.

Miscall and Holder<sup>39</sup> report 22 cases with primary union, utilizing musculofascial flaps, but admit that "insufficient time and observation, also the number of cases, do not permit any statement in regard to the rate of recurrence"

Hamilton, Custer and Kellner<sup>40</sup> in an analysis of 132 consecutive cases, find a 53 per cent failure in cases with a history of recurrent discharge or previous abscess formation, in addition to symptoms eight weeks prior to examination

Larkin<sup>41</sup> claims 90.9 per cent cures by his modification (a narrow strip of skin is removed in the midline (often no more than 0.5 cm in width). A block excision is effected through this space. No 30 stainless-steel sutures are placed 1.2 cm apart under the gluteal and sacrococcygeal fascia, after

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which 15,000 units of penicillin is administered every three hours until the eighth postoperative day.

Lahey<sup>3</sup> has conceived his own flap method. After block excision, a lateral incision is made parallel to one edge of the wound. Beneath this a bridge of skin and subcutaneous fat is separated from the gluteus maximus muscle so that the flap moves freely to the opposite side. The fat-lined bridge of skin is then displaced to the midline and sutured to the opposite edge of the wound to hold it in place. The defect resulting from transference of the flap is packed with gauze and allowed to close by granulation. When the resulting defect is small, Lahey brings the edges together.

Swinton,<sup>4</sup> using the Lahey method in 23 cases obtained 35 per cent recurrences, finding it difficult to prevent infection.

#### *Partial Closure*

The two chief exponents of the partial-closure method are MacFee<sup>5</sup> and McCutchen.<sup>6</sup> The former states that the principal drawback of primary closure is the constant presence of infection and difficulty in obliterating dead space. After removal of the diseased tissue, partial wound closure is effected by suturing of the skin edges to the sacrococcygeal fascia and underlying ligamentous structures, the skin edge on each side is brought as near to the midline as possible without tension, black silk sutures being used and a narrow undercovered area of fascia being left between. Furthermore, if the area is large enough to warrant it, he recommends a skin graft.

McCutchen,<sup>6</sup> while using the partial closure method, attempts to save skin in so doing two sides of a triangle are made on each side of the natal cleft, with the apex about 2.5 cm. from the midline and with either limb about 3.7 cm. in length. The apexes are joined across the midline by another incision (through the skin only), the lower flap is undermined to a point well below the coccyx, and the upper flap to a point well above the sacrum. The lateral flaps are formed by undermining of the incomplete triangles down to their bases, 5 gm. of sulfonamide powder is inserted, and stab wounds are made in all flaps, thus providing drainage for potential or actual infection. McCutcheon states that close apposition of the wounds is not desirable and that gross infection has appeared in a large percentage of his wounds.

#### *Open Method*

In the open method, all sinus and cyst tissue is excised, the wound being permitted to heal in by granulation. Smiley<sup>7</sup> favors the open method, with sclerosing solutions for the less complicated cases.

Carrington<sup>8</sup> performs subcutaneous excision beneath definitely placed flaps. The incisions are placed so that the bases are at right angles to the

long axis of the body (two to five such flaps), a midline scar being thus avoided.

Swinton<sup>4</sup> has performed operations in 85 cases via the open method in the past ten years, with a recurrence rate of 18.7 per cent.

Burns,<sup>9</sup> in a series of 240 cases, found 70 per cent cured by one operation, with a great majority cured by two operations.

Zieman<sup>10</sup> obtained cures in 100 per cent of cases with the open method, using wide excision, with an average stay in the hospital of two days.

Kleckner,<sup>11</sup> in a series of 160 cases, reports 100 per cent cures. In a questionnaire that he sent to fellows and associates of the American Proctologic Society (of which 75 per cent answered), 87 per cent were in favor of the open method, 75 per cent favored the closed method, and 55 per cent were undecided, using both open and closed methods. From the standpoint of cure, recurrence and safety, 70 per cent stated that there was no better method than the open one.

Tendler<sup>12</sup> stresses postoperative care: he repacks the cavity until the patient is discharged from the hospital, and insists on utmost cleanliness during the packing period. The patient is up on the fourth day and home in seven or eight days, and when the wound cannot hold packing, Sitz baths are instituted. Tendler is against too much activity, sitting or lying on the area after operation, poor hygiene and careless dressings. Tendler's cases heal in six weeks to two months.

#### *Discussion*

A glance at the highlights of the various technics impresses one with the fact that, regardless of the method employed, the average healing time, in sufficiently large series of cases, is anywhere from one to three months. When the healing time has been spectacularly shorter, one must assume that the lesion was small, confined and of limited infection, longer healing is assumed to be due either to faulty healing or technic or to more extensive disease.

Treatment with roentgen-ray therapy is inconclusive, and requires further investigation and a much larger presentation of cases before any definite conclusion can be reached.

The sclerosing method appears to have some merit in the self-limiting cases but hardly seems suitable for patients with a fairly long history of infections with lateral tract extensions. Although neurologists have been eminently successful in fixing the walls of gliomatous cysts with sclerosing solutions and various similarly acting solutions have been successful in the treatment of internal hemorrhoids and varicose veins, one fact seems to stand out in these categories: the lesion is sterile, whereas in pilonidal cysts and sinuses one is dealing with tissue that is basically infected. As in roentgen-ray therapy, the number of cases presented



by any particular therapist is quite modest (3 to 6), with only a relatively larger number studied by two authors (Heyd,<sup>18</sup> 25 cases, and Shafiroff and Doubilet,<sup>19</sup> 27 cases)

Marsupialization seems to offer no especial advantages. On Buie's<sup>24</sup> premise that the "deeper half of the lining of the cyst cavity, since it was originally intended to form skin, can be used to advantage in the surgical management of the problem," and Van Dyke's<sup>27</sup> statement that "since the cyst is ectodermal in origin, it will now perform its pre-designated duty as skin," one should expect 100 per cent cures. Unfortunately such a result is not obtained—and through no fault of the surgeon performing this technic. Two observations tend to modify the tenets of Buie and Van Dyke: the consensus on etiologic research (Gage<sup>4-6</sup> and Fox<sup>10</sup>) is that the lining of the cystic cavity can produce primitive skin appendages only, and the cyst cavity is usually infected. According to Van Dyke "infection in this area is the rule, and this may result in swelling of the tissues and cutting through of the sutures", Buie states that "if there has been no destruction by inflammation or erosive changes within the walls of the cyst or sinuses, then the cavity can be used to advantage in the surgical management of the problem." One must acknowledge that the cavity is usually infected, and this fact tends to vitiate the case for marsupialization.

So far as the use of the cautery knife is concerned, whether for the open or the closed method, I am not convinced of its superiority over the ordinary scalpel. One cannot get the same "feel" in cutting away infected, grumous or scarred tissue with the cautery as with the scalpel, the discoloration subsequent to cauterization beclouds the color of the healthy, yellow fat at the point where one stops the excision, and the coagulative effects may block off the openings of the lateral tracts, leaving them untouched.

The field, therefore, is thus narrowed down to the open versus the closed (including partial closure) method. Just as in the cases of roentgen-ray therapy, sclerosing solutions and marsupialization technic, the early and mildly infected cases may respond to the closed method. Since a patient ordinarily does not come to the surgeon for mere excision of a sacrococcygeal dimple or dimple sinus, one must conclude that the cases operated on are infected and that the surgery of pilonidal cyst and sinus is the surgery of infected tissue.

The ingenious devices of various sutures and gluteal flaps to eliminate dead space and to effect good primary closure bear eloquent testimony to the fact that something is basically wrong with the closed method. In other words, one carefully removes all apparently infected tissue and then carefully proceeds to close the wounds up—a process that the particular surgeon would never consider in surgery of infected tissue elsewhere in the body,

and with apparent disregard, as Nesselrod<sup>29</sup> so aptly puts it, of the "nearness of the operative field to the anal canal with its ducts, lymphatics and glands, and of the harboring of infection in the lymphatics adjacent to the sinuses and cyst itself." One obtains drainage and then fights to prevent egress of inflammatory products and finally broods about the recurrences.

The only hope for freedom from recurrence and of obtaining a good mechanical result, in case after case, lies in the open method. In performing the open operation, it is not necessary to remove large blocks of healthy skin and subcutaneous tissue, for it is then that delayed healing and a painful, tense scar occur, with the firm resolve that the next time, if it is done in the same manner, the operator will be sure to make up the defect by transposition of a gluteal flap or a specially devised suture placement. Similarly, a medical excision via the open method is likewise doomed to failure.

I believe that it is dangerous to employ a local anesthetic, for the needle is bound to drive inflammatory products into healthy zones. The interdiction against caudal anesthesia should certainly hold true for local infiltration. And it is just as well to interpolate that if the operation is not executed properly, the most meticulous aftercare, such as confining of the bowels, keeping the patient prone in bed for days on end with the legs straight, avoiding resting on the wound, blocking off the anus and supplementing with penicillin and sulfonamides, will all go for naught.

Except for the extremely rare cases of embryologic involvement of the neural canal through the sacrum, one should obtain 100 per cent cures by means of a properly performed open operation.

#### THE OPEN OPERATION

The method I use is based on a successful experience of twenty-two years. I do not claim it to be original with me. It is quite probable that others use a similar technic with their own personal modifications. With the procedure followed, there have been no known recurrences.

With the patient in the Depage position, and the buttocks spread via broad adhesive bands extending out to the edges of the table, one makes a longitudinal incision along the midline over the diseased area and then develops it until the sacrococcygeal fascia is reached. The length of the original incision is gauged by the external signs of the lesion. The incision can always be enlarged, consistent with the extent of the diseased tissue found on opening of the cavity. The one skin edge and wall is grasped with several Allis forceps, and the skin thus pulled back and everted. With the forceps as traction, all grumous, infected, scarred and discolored tissue is dissected out until healthy, yellow fat is seen on the wall. During the dissection, one looks for lateral tracts by observing small discolored areas in a field

of healthy fat. These areas should be probed and excised. The other skin edge and wall are similarly treated. If the fascia looks clean, it is left alone, if discolored in spots, those areas may be scraped. All the forceps are then removed, followed by a falling together of the skin edges of the wound. An Allis forcep is placed at either end of the incision, being held by an assistant so as to render the wound taut. The wound is saucerized symmetrically in an elliptical manner as follows: an elliptical piece of skin and subcutaneous tissue is removed from either skin edge along its entire length according to the size of the cavity. The widest portion of the ellipse is anywhere from 0.5 to 1.5 cm., with an average width of 1.2 cm.

There is then a wedge-shaped wound, narrowest at the bottom, widest externally, with all discernible diseased tissue removed. The wound is packed lightly with vaselized iodoform gauze, which is removed on the following day and never replaced. Hot Sitz baths twice daily are instituted on the first postoperative day. The patient may lie in any position in bed, and the bowels are not confined, any soiling being washed away with Sitz baths. The patient is up and around on the first postoperative day.

With a gloved finger, the bottom of the wound is broken up daily for the first few days and then less frequently as healing progresses, to prevent false closing or bridging over of granulation tissue. If the granulations are flabby or grow too fast on one side or the other, especially toward the external portion of the wound, they may be shaved down by the application of dipped 75 per cent silver nitrate applicators to the surface. Subsequent dressings consist of gauze, the inner surface of which is spread with vaseline to prevent sticking, and then a combine, all held in place with a T binder. The patient may go home in three or four days and may return to work in seven to ten days, depending on the wound size. Further postoperative care is continued in the office at the convenience of the patient in relation to his working hours.

If the operation is not a mutilating one — and there is no reason why it should be — the wound will close according to the extent of the lesion, in the usual one to three months, with a surprisingly small width of smooth, postoperative scar tissue.

The wound having been arranged rationally, there should be no difficulty in obtaining progressive closure. One should bear in mind that the gluteus maximus muscles act as effective purse-string sutures.

### SUMMARY

A review of the literature of the past fifteen years on pilonidal cyst and sinus is presented, delineating the highlights of the various techniques. A critical analysis of these methods is attempted, with the hope that the thoughts thus provoked may initiate a reorientation in the treatment of this pathologic entity. In addition, a technic is presented by which 383 cases have been treated over a period of twenty-two years with no known recurrences. The shortest healing time has been two weeks, and the longest fifteen weeks.

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 34241

#### PRESENTATION OF CASE

*First admission* A forty-three-year-old type-setter entered the hospital because of epigastric pain.

Four years previous to admission he developed epigastric pain, hematemesis and melena. He was treated at another hospital for an ulcer though none was seen on x-ray examination. He obtained little relief of pain. In the two months before admission the pain became worse and was accompanied by vomiting.

When eight years old the patient had "rheumatism," and at about the age of fourteen years he developed a left upper, dorsal and a right lower dorsal scoliosis and a lumbar lordosis. Since then he had worn a brace intermittently. Six years before admission he had an attack of pleurisy, and several other attacks had occurred since then. Four years before admission he had an attack of pneumonia.

Physical examination revealed nothing remarkable except moderate emaciation and marked right dorsal scoliosis with rotation and prominence of the right chest posteriorly. There was some lumbar lordosis.

Examination of the blood disclosed 15 gm of hemoglobin and a white-cell count of 7200. The urine was normal. The stools were guaiac positive but later became negative. An x-ray film showed a deformed duodenal cap. The lung fields were clear.

The symptoms subsided on an ulcer regime. The patient was discharged improved after two weeks in the hospital.

*Second admission* (seventeen months later) The patient was followed in the Out-Patient Department and did fairly well for nine months, when he developed a cough and raised considerable sputum, some of which was bloody. There were no chills or fever. A pleural friction rub was audible over the right anterior chest. An x-ray film showed pleural thickening of the right lower lateral chest and an area of increased density anteriorly above the middle third of the chest, apparently in the right lung field. The sputum was negative for acid-fast organisms. The patient improved with bed

rest, the cough disappearing, but a pleural friction rub was audible for several weeks. He failed to gain weight and was weak but was eventually able to return to work.

Ten days before admission he developed a "head cold," which was accompanied by a cough. There was moderate sputum, at first rust-colored but later yellow and tenacious. Three days before admission he felt worse and became dyspneic and much weaker. A doctor gave him penicillin by mouth, but he felt no better and came to the hospital.

Physical examination revealed severe kyphoscoliosis (upper left and lower right dorsal, with rotation of the left chest dorsally). There was dullness over the lower lobe on the right, with diminished breath sounds. The breath sounds were bronchial in character over the right upper lobe. The left lung was normal. The heart was displaced to the left, and the pulmonic second sound was greater than the aortic second sound.

The temperature was 98.2°F, the pulse 95, and the respirations 20. The blood pressure was 105 systolic, 65 diastolic.

Laboratory examination showed a normal urine. Examination of the blood disclosed a hemoglobin of 16 gm and a white-cell count of 13,400, with 86 per cent neutrophils. The sputum was negative for acid-fast bacilli. Cytologic examination of the sputum was reported positive for tumor cells. X-ray films of the chest showed fluid in the right pleural space and increased density in the right upper chest, which appeared most likely to be consolidation in the right upper lobe.

The patient improved on penicillin. One hundred and seventy-five cubic centimeters of amber fluid was removed from the right chest. This had a specific gravity of 1.022 and contained 15,000 cells per cubic millimeter, of which 6750 were white cells. Some of the cells with Wright's stain resembled the cells in the sputum. A gallop rhythm developed, digitalis was given. The patient was discharged slightly improved on the fifteenth hospital day.

*Final admission* (fifteen days later) The patient grew weaker and was awakened at night by shortness of breath, which was relieved when he sat up. There was slight cough and almost no sputum. He had been taking 0.1 mg of digitoxin daily.

Physical examination showed cyanosis. The neck veins were distended and pulsating. There was moderate edema over the lumbar region. There was flatness over the right chest, with decreased breath sounds and tactile fremitus over the lower half. There were medium rales at the left base. The heart was enlarged, the border of cardiac dullness extending 10 cm to the left, with a strong point of maximum impulse. The rate was 120 with a regular rhythm.

The temperature was 98.2°F, the respirations 25, and the blood pressure 130/70.

The hemoglobin was 15.5 gm., and the white-cell count 15,400, with 87 per cent neutrophils.

Three hundred and ninety cubic centimeters of turbid, amber fluid was removed from the right chest in the Emergency Ward on the day before admission, and 700 cc. of similar fluid on the day of admission. The specific gravity of the fluid was 1.012. Following the tap the respirations became more labored, and the patient became comatose. He died on the day after admission.

### DIFFERENTIAL DIAGNOSIS

DR. MYLES P. BAKER: The first hospital admission eighteen months before death led to the following findings: duodenal deformity compatible with duodenal ulcer, probably active to judge from the presence of occult blood in the stools, persistent pain and vomiting, clear lung fields by x-ray examination, and pronounced dorsal kyphoscoliosis, with a story of repeated attacks of chest pain and one bout of pneumonia, such as these hunchback people are prone to develop. Deformity of the thoracic cage is most likely attributable in this case to poliomyelitis at the age of eight, with increasing scoliosis up to the time of adolescence, when fixation occurred. We hear no more about the duodenal ulcer, and I doubt if it had anything to do with the terminal illness. Nine months later he developed cough, — a new symptom, — with bloody sputum. X-ray study of the chest revealed a pleural process on the right side and a lesion in the right lung field as well. He made hard weather of it, with halting improvement, and obviously was losing ground.

An acute respiratory type of infection brought him to the hospital, with dyspnea, physical signs of fluid at the right base and consolidation or atelectasis with an open bronchus in the right upper lobe. X-ray studies confirmed the physical findings.

Three ominous findings appear on the second admission: the tumor cells in the sputum, similar cells in the pleural fluid, which contained red cells, and gallop rhythm. A man with a large pleural effusion and a displaced heart often has tachycardia and sometimes a suggestion of gallop rhythm. In this case it was considered serious enough to institute digitalization, so that I think the gallop rhythm was probably important and represented the "cry of the heart for help." It indicated probably myocardial damage and dilatation of the heart. The diagnosis in this case depends, I think, on two things — the appearance of the chest x-ray film, particularly regarding this shadow in the right lung field, and the "tumor cells" in the sputum and possibly in the pleural fluid. (Was this a Vincent Laboratory or a house officer's diagnosis?)

DR. TRACY B. MALLORY: Mrs. Graham, do you know about that?

MRS. RUTH GRAHAM: The report on the sputum was from the Vincent Laboratory.

DR. BAKER: I think it will be well to look at the x-ray films.

DR. STANLEY M. WYMAN: The first series of films shows the marked scoliosis described. The heart shadow cannot be adequately examined because of the chest deformity. The lung fields appear grossly clear on initial examination. Almost a year later another set of films shows no definite change except that one wonders about a little shadow of density extending outward from the right lung root. The films taken ten days later show an area of density extending in fan shape and involving the base of the right upper lobe. Some density is seen in the posteroanterior view. One cannot, however, see the bronchi adequately to determine whether or not there is occlusion of the major bronchi. This process continues in the subsequent films, with some collapse and areas of increased, rather spotty, mottled density in the right upper lobe. In some of the early films fluid is seen in the right pleural cavity. The last examination shows a large quantity of fluid occupying the right pleural space, and the right upper lobe is still further decreased in size. The density in the right upper lobe is hazy in character. This film shows unusual prominence of the pulmonary artery, in keeping with the finding of an increased pulmonary second sound. It is hard to tell about it because of the chest deformity.

DR. BAKER: Is the thoracic cage small?

DR. WYMAN: I think if measured volumetrically, it would be smaller than usual. Again, it is hard to say because of the deformity.

DR. BAKER: In this photograph that I have of the patient he looks much smaller from the diaphragm up than down.

I am told that the Vincent Laboratory has a very interesting absence of false positive cytologic diagnoses of cancer in examination of sputum specimens. In 5 or 6 cases the cytologic diagnosis has been an important primary indication of the diagnosis. Generally, of course, it has been confirmatory in proved cases of malignant tumor. It seems to me that with the x-ray picture of a hilar process producing atelectasis of the right upper lobe and the positive cytologic report from the laboratory we have good grounds for assuming that this man had bronchiogenic carcinoma to add to his serious handicap of kyphoscoliosis.

The question remains concerning the manner of death. We know that a year previously the chest film was clear. If we make the diagnosis of bronchiogenic carcinoma — a slowly growing tumor — as the sole cause of death, the patient died early. Was the manner of death in keeping with the diagnosis of pulmonocardiac failure described by Chapman\* in 1939? Some of the features of this patient's

\*Chapman, E. M., Dill, D. B., and Graybiel, A. Decrease in functional capacity of lungs and heart resulting from deformities of chest; pulmonocardiac failure. *Medicine* 18:167, '32, 1939.

death are so characteristic of this entity that I think it is worth elaborating upon briefly. It is pointed out by Chapman et al. that once these patients begin to fail, they survive only a short time, averaging about five months. This patient died within one or two months of the onset of symptoms of failure. At the last admission the picture was that of congestive failure—distended neck veins, edema over the back, rales at the left base, right pleural effusion and tachycardia. In these kyphoscoliotic persons habitual dyspnea is the rule—more so than the history indicates in the case under discussion. We do know that he was able to work only sporadically and felt weak prior to the second admission, he may have been dyspneic as well and taken that for granted over the years. Tachycardia is common, and edema rare and terminal, the accentuated pulmonic second sound is an outstanding physical finding. This man had it. There are no typical murmurs in this particular symptom picture. Cardiac enlargement, which I believe he had, is difficult to be sure about because of the chest deformity, as Dr. Wyman has said. Electrocardiograms are notably normal in the majority of cases and bronchial infections are rather common in these handicapped people and very likely, as in this man, to be one of the features that tip the very precarious balance in favor of failure. Digitalization and the use of diuretics are characteristically fruitless with such a handicapped pulmonary function, already diminished by bronchial infection. This is just the sort of added load that produces pulmonocardiac failure in such a patient. I think the findings in this case support such a hypothesis. The patient was singularly ill suited for the development of bronchiogenic carcinoma. The first manifestations of pleural irritation, as well as the development of pleural fluid and bronchial infection, in an atelectatic lung, were more than enough to tip the balance in favor of pulmonocardiac failure. I think that autopsy will show small lungs with evidence of acute bronchitis and parenchymal infection, congestive failure, probably a dilated right ventricle and bronchiogenic carcinoma.

DR. MALLORY: Dr. Bland, what did you think about this case?

DR. EDWARD F. BLAND: I happened to be in charge when the patient was on the ward, and in retrospect there were several remarkable things that it might be interesting to call attention to. Apparently we were so engrossed with what was going on in the lungs that an electrocardiogram was not taken. I do not believe that it would have clarified the situation because it probably would have been normal, as Dr. Baker has suggested, except for tachycardia. When the patient came in he was quite ill. The first impression both on the ward and in the Pulmonary Clinic where he was seen was that of an acute pulmonary infection, which improved temporarily with penicillin. However, he

continued quite ill. Since we could not find acid-fast bacilli in the sputum we asked the Vincent Laboratory to examine the sputum and the chest fluid. The report on the sputum came back with the unequivocal diagnosis of tumor cells. Other sources of opinion were not so certain that they were tumor cells. We asked the Pulmonary Clinic to review the situation in the light of the sputum findings. At that stage, in spite of the positive cytologic evidence of cancer, the Pulmonary Clinic was not convinced about the presence of tumor. One might wonder why bronchoscopy was not performed. That seemed inadvisable because of his poor condition and the marked deformity, as well as an element of heart failure. Why did we not give some form of treatment? Estrogens were contraindicated because of the congestive failure, and we did not want to waterlog the patient any further with sodium retention. X-ray therapy was considered and discarded by the Tumor Clinic. Therefore, since he was reasonably comfortable we let him go home and asked him to return if he became more uncomfortable, which he promptly did.

DR. F. DENNETTE ADAMS: Would this electrocardiogram not show right-axis deviation because of the deformity of the chest?

DR. BLAND: About a fifth of the cases show right-axis deviation.

DR. MALLORY: Mrs. Graham, have you anything to say?

MRS. GRAHAM: No, except that smears of the sputum were definitely consistent with epidermoid carcinoma.

#### CLINICAL DIAGNOSIS

Kyphoscoliotic heart disease  
Bronchiogenic carcinoma?

#### DR. BAKER'S DIAGNOSES

Pulmonocardiac failure ("scoliotic heart disease"),  
with right ventricular dilatation  
Kyphoscoliosis, dorsal, severe  
Bronchiogenic carcinoma

#### ANATOMICAL DIAGNOSES

*Bronchiogenic squamous-cell carcinoma, right upper lobe*  
*Kyphoscoliosis*  
*Cor pulmonale*  
Pulmonary abscess  
Bronchiectasis, right upper lobe  
Pulmonary atelectasis

#### PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination showed bronchiogenic carcinoma of the right upper lobe. This man was not a person who could have been subjected to bronchoscopy, although it would have been very easy to obtain a biopsy since the tumor had extended into the right primary bronchus.

There was the severe thoracic deformity that has been described, and there was very little useful pulmonary tissue at the time of death. The right upper lobe showed beyond the obstructed bronchus an abscess cavity and also rather diffuse bronchiectasis. There was marked collapse of both lower lobes, so that the patient had very little except the left upper lobe with which to breathe. There was pleural effusion—not much—about 200 cc on each side, but with his small chest that was significant. The heart was slightly hypertrophied, particularly the right ventricle, which was dilated and, nevertheless, had a thickness of 6 mm.

It certainly seems as if an electrocardiogram should have shown right-axis deviation if it had been obtained. There were no metastases except to the regional lymph nodes at the hilus, so that I think Dr Baker's prediction is correct that cancer was not the cause of death but it was the acute pulmonocardiac failure that one sees so regularly with this type of chest deformity.

There was one puzzling feature: the liver showed granulomas, which I could not identify. They did not look much like tubercles. The microscopic sections were negative for acid-fast bacilli. I think that he did have a terminal infection, which I could not identify. Post-mortem cultures showed a mixture of colon bacilli and nonhemolytic streptococci, probably a contaminant rather than anything significant.

DR BENJAMIN CASTLEMAN: What type of carcinoma?

DR MALLORY: It was a well differentiated squamous-cell carcinoma.

DR BLAND: Did he have a gastric ulcer?

DR MALLORY: None that we could find. He had a dilated esophagus suggesting cardiospasm, which sometimes produces symptoms similar to those of a gastric ulcer.

A PHYSICIAN: You say that there were no metastases except to the hilar lymph nodes—no evidence of pleural involvement? I ask because of the fluid findings.

DR MALLORY: No, we did not find any pleural involvement.

## CASE 34242

### PRESENTATION OF CASE

A seventy-nine-year-old widow was admitted to the hospital because of shortness of breath and chest pain.

The patient complained of pain beneath the left breast nine days before admission, and three days later the pain became severe, radiated down the left arm, and was accompanied by shortness of breath. A physician found the blood pressure to be 138 systolic, 60 diastolic, the pulse was 100 and regular, and there were basal rales and slight edema

of the ankles. An electrocardiogram taken on the following day showed normal sinus rhythm, small Q waves in Leads 1 and 2, a small R wave, a secondary R wave and a deep S wave in Lead 3. The T waves in Leads 1 and 2 were upright, and the T wave was upright but diphasic in Lead 3. The patient also complained of pain in the right thigh. The symptoms subsided with bed rest, digitalis and diuretics. Thirty-six hours previous to admission the dyspnea and pain in the left chest recurred. These gradually became worse and were accompanied by cyanosis and several episodes of vomiting.

The patient had been hospitalized nine, eight and seven years before admission because of what the family thought were heart attacks. Four months before admission she was seen by the family physician, who found moderately advanced congestive failure and a blood pressure of 180 systolic, 100 diastolic. She complained of backache, but an x-ray film showed only osteoporosis. Six weeks before admission the patient underwent an appendectomy at another hospital. The diagnosis was acute suppurative appendicitis. The postoperative course was uneventful except for a staph abscess.

Physical examination revealed a disoriented, cyanotic woman. The neck veins were distended and pulsating while she was in a semierect position. The heart was slightly enlarged. There was a slight apical systolic murmur. The aortic second sound was equal to the pulmonary second sound. The breath sounds at the left base were less distinct than those on the right. There was diffuse tenderness in the right lower abdomen, with a healing staph abscess in the appendectomy scar.

The temperature was 101.2°F, the pulse 80, and the respirations 32. The blood pressure was 135 systolic, 55 diastolic.

Examination of the blood revealed a hemoglobin of 13 gm and a white-cell count of 16,400, with 84 per cent neutrophils. The nonprotein nitrogen was 49 mg and the serum protein 7.02 gm per 100 cc. The urine gave a ++ test for albumin, and the sediment contained 1 or 2 pus cells and numerous hyaline casts per high power field. X-ray films of the chest with the patient recumbent showed unusual prominence of the right pulmonary artery, and the linear markings were less numerous on the right than on the left. There was a suggestion of an abrupt termination of what might have been the pulmonary artery on the right. There were irregular areas of density in the upper lungs with some calcification. There was an area of irregular, strand-like density at the left base, with obscuration of the left costophrenic sulcus. There were hypertrophic changes in the thoracic spine, with some increase in the anteroposterior diameter of the chest. A film of the abdomen was not satisfactory. An electrocardiogram showed normal rhythm, a PR interval of 0.2 second, a normal

axis and small Q waves in Leads 1,  $V_4$  and  $V_5$ . The ST segments were depressed in Leads 1, 2, 3, VF,  $V_2$ ,  $V_4$  and  $V_5$ , the T waves were inverted in Leads 2, 3, VF and  $V_2$  and seminverted in Leads 1,  $V_4$  and  $V_5$ .

On oxygen the patient became much less dyspneic. She was given digitalis, ammonium chloride and penicillin (300,000 units daily). The temperature returned to normal. An x-ray film of the chest taken on the seventh hospital day showed less prominence of the right pulmonary artery, although again there was a suggestion of diminution in the vascular markings in the lower portion of the right lung field. There was an area of density at the left base. There was little change in her condition until the eighth hospital day, when she suddenly collapsed. The blood pressure was 100 systolic, 50 diastolic, and the pulse 90 and totally irregular. She complained of substernal pain. An electrocardiogram showed a different rate of auricles and ventricles, which was probably due to digitalis toxicity. On the following day she was worse, but the neck veins were not distended and she was not cyanotic. The abdomen became distended and diffusely tender. A stool specimen was guaiac positive. She became unresponsive and died on the tenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR EDWARD F. BLAND: The perspective of the abstract as read is slightly confusing, and hence it seems worth while to recapitulate the more important events. We are presented with a seventy-nine-year-old woman, who had an indefinite history of what was thought to be heart attacks seven, eight and nine years previously, perhaps they were heart attacks, but she got along very well otherwise until near the end of her life. The terminal illness began about four months before entry to the hospital, when she was found to have moderate hypertension and congestive failure. The latter seemed to respond to therapy until six weeks before entry. At that time she developed an acute condition of the abdomen, which required operation and a suppurative appendix was found and removed. Nine days before entry she had sudden pain in the left chest, with dyspnea and also pain in the right thigh—nothing more is said about the legs, however, from then on. An electrocardiogram was uninformative, being consistent with an aging heart and perhaps a digitalis effect. This sudden chest pain, it seems to me, must have been due to a pulmonary infarct. She might have had a myocardial infarct, but the symptoms are more suggestive of trouble in the lungs than in the heart. She again did well until thirty-six hours before entry, when a similar attack came on abruptly, which again sounds more pulmonary than cardiac. From then on she progressed slowly downhill. On entry she was a very aged and a very ill woman, with evidence of congestion and mild uremia. She was

febrile and had a suspicious tenderness in the right lower quadrant. The legs are not mentioned, I would be interested to know if they were all right.

DR HELEN S. PITTMAN: They were.

DR BLAND: The X-ray Department made some interesting comments. The films were probably taken with a portable machine, but they must have been unusually good to permit the observations recorded above. We had better look at them.

DR STANLEY M. WYMAN: We have two series of films, the second examination being done two days after the first. These interpretations were made by Dr. Joseph Hanelin of our department, and I think his observations were very astute. The right main pulmonary artery is seen at this point, the lower margin is unusually sharply defined and clear-cut. It seems to have a lobulated termination quite in contrast to the usual lower termination of the pulmonary artery. The fine mottling and calcification in both upper-lung fields are probably of long standing. The areas of linear density and the fibrosis at the left base are probably old. There seems to be in the entire right lower-lung field a paucity of vascular markings in comparison to the left. This is a valid observation although the patient is slightly rotated. The chest is considerably increased in the anteroposterior diameter, suggesting some degree of emphysema.

DR BLAND: The heart is not very large, is it?

DR WYMAN: It is impossible to measure it accurately. The patient was lying down. The measurements in this position would make the heart about 13 cm. as compared with 22 cm. for the chest.

DR BLAND: The left lung is smaller than the right?

DR WYMAN: That is due to rotation of the chest cage.

DR BLAND: The lung roots are dense, with abrupt cessation of the right main pulmonary artery shadow?

DR WYMAN: I believe that is so. The left main pulmonary artery does not show such a configuration. The second film shows considerable change in the right main pulmonary artery, again suggesting termination there. This film shows the large fibrotic process at the apex.

DR BLAND: There is nothing new in the second film—just a little fluid at the left base perhaps.

DR WYMAN: I do not feel safe in thinking that is the costophrenic angle posteriorly. It seems to be sharp on both sides. The films of the abdomen, which were taken with a portable machine, show no gross abnormality.

DR BLAND: It would have been helpful if she had been well enough for fluoroscopy because the right pulmonary artery is enlarged and ends abruptly—it must be obstructed at that point.

DR WYMAN: It looks unusual.

DR BLAND: It would be helpful to know if it pulsated.

Dr WYMAN That is pretty essential

Dr BLAND During the hospital stay the patient was treated for heart failure and infection. Nevertheless, she slowly worsened and went into a terminal collapse of some sort with arrhythmia of the heart, and died two days later. These terminal events were interesting. Was this abdominal film taken at the end?

Dr WYMAN It was taken about two days before death.

Dr BLANN The clinical picture is complicated by the septic appendix, which was removed, and the suspicious persistence of tenderness in the abdomen, the terminal distention, diffuse tenderness and a positive guaiac test on the stools. Nothing is said about a tender liver, and the veins were not engorged when the abdomen was becoming distended. Therefore, hepatic congestion was not responsible. The other possibility is mesenteric thrombosis or embolism, with intestinal infarction. Also, as a result of that or possibly as a result of a residual infection from the appendix, peritonitis must have developed terminally.

In conclusion, therefore, this patient had hypertension and coronary-artery disease. Congestive failure seems to have been definite, and I believe she also certainly had pulmonary infarcts. Other complications are probable but seem somewhat less well defined. I am intrigued by the x-ray appearance of the right hilus. She must have had a thrombus obstructing the right pulmonary artery. Furthermore, she probably had old myocardial infarcts, from the history she might even have had a recent one, but we cannot prove it from the electrocardiograms. I think that something acute was going on in the abdomen at the end, being due, I suspect, to a mesenteric thrombus or embolus, with intestinal infarction.

We might mention in passing that when elderly people die in this fashion there are two things that sometimes turn up as unexpected findings. One is bacterial endocarditis. I do not believe that this patient had that. The other point that one should keep in mind in the face of progressive thrombophlebitis and pulmonary infarcts is a malignant tumor in the abdomen. We have no right to make such a diagnosis on the data given.

Dr F DENNETTE ADAMS Dr Bland, in the presence of pulmonary infarction—which you believe was present in this case (and I do too)—what is your evidence for congestive failure? Do you have to add congestive failure to account for the picture if you assume pulmonary infarction?

Dr BLANN The most suggestive finding is the swollen neck veins, which seemed to be definite when she came in. Is that correct, Dr Pittman?

Dr PITTMAN Yes.

Dr BLAND Her physician made a diagnosis of heart failure four months before the acute episode

here. The heart, however, on x-ray examination, did not look like it.

Dr ADAMS Can distended neck veins occur with pulmonary infarction?

Dr BLANN They may, with massive pulmonary embolism.

Dr PITTMAN The original note says that the patient was sitting up in bed with gasping respirations and that the neck veins were distended and pulsated in both clavicles in a semierect position.

Dr BLANN In view of this I think we must assume an element of heart failure. We do not know about the liver. People with swollen neck veins from heart failure have large livers too.

Dr ADAMS May I ask one other question?

Dr BLANN Yes, but do you think she did or did not have congestive failure?

Dr ADAMS I do not feel sure about it. I would stick to pulmonary infarction. She may well have had peritonitis, I am always suspicious of the diagnosis of stitch abscess.

Dr WYMAN RICHARDSON There is no mention that anyone looked at the blood smear to see if she had neoplasm or infection.

Dr ADAMS I think she might have had both—probably acute peritonitis, which in older people is so often overlooked.

Dr PITTMAN This was a difficult problem. The patient was an old and very sick woman in whom the history and the findings were very confusing. We deliberated long on the morning following admission regarding whether the more reasonable probability was myocardial infarction or pulmonary infarction, at that time she had some cyanosis, a fall in blood pressure, transient leukocytosis, then a white-cell count of 6000, no change in breath sounds and no elevation of the respiratory rate, so that I leaned to the side of a myocardial rather than a pulmonary process as the basic disease. Five days later she had been got up in a chair for a few minutes, but she suddenly felt weak, the legs collapsed, at that time the heart rhythm had become irregular, and she was gasping and complaining of a very severe pain substernally. We thought that it might be another myocardial infarction or might very well be a pulmonary infarct. In the next thirty-six hours the signs and complaint shifted completely from above the diaphragm to the abdomen. She had a silent abdomen. It was very tender and she began to produce guaiac-positive material whereas previously it had been guaiac negative. We believed that mesenteric thrombosis was the most reasonable explanation. She died very quickly after this abdominal episode, and the house officers at the time of death put down the diagnosis as question of coronary thrombosis, question of pulmonary embolus and question of mesenteric thrombosis.

Dr BLANN Would it be unusual, Dr Mallory, for a patient of this age, after a four months' ill-



ness in and out of bed, to turn up in your department without a pulmonary embolus?

DR TRACY B MALLORY I think most of them would have one

#### CLINICAL DIAGNOSES

Coronary thrombosis?  
Pulmonary embolus?  
Mesenteric thrombosis  
Arteriosclerotic heart disease.  
Congestive failure

#### DR BLAND'S DIAGNOSES

Hypertension and coronary-artery disease  
Pulmonary infarcts  
Thrombosis, right pulmonary artery  
Mesenteric thrombosis (or embolism)  
Peritonitis?

#### ANATOMICAL DIAGNOSES

*Pulmonary emboli, multiple*  
*Thrombi of right ventricular endocardium*  
*Thrombosis of left popliteal vein*  
Myocardial infarction, very recent  
Segmental gangrene of bowel  
Arteriosclerosis, generalized, severe  
Cholelithiasis

#### PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed multiple pulmonary emboli of varying ages. There was complete blockage of the right main pulmonary artery, as the X-ray Department had predicted. A great many of these emboli had evidently been present from days to weeks since considerable degrees of organization were present. The heart weighed 360 gm — slight hypertrophy for a woman. The right ventricle contained thrombi behind and around the columnae carneae. These were adherent, and microscopical examination showed that they, too, were partially organized. There was also an area of acute hemorrhagic discoloration in the interventricular septum. This, however, was evidently fresh and

acute in contrast to the intracardiac thrombi, which must have been present for a much longer period. A second possible source of the emboli was the popliteal vein on the right, where there was some thrombotic material. We could not say with certainty whether the emboli found in the lungs came from the leg veins or from the right side of the heart. The coronary arteries were not sclerotic but appeared wide and capacious, remarkably good in view of her age.

The bowel showed a segment of acute hemorrhagic enteritis with hemorrhagic necrosis of all layers of the wall. This was 22 cm long, but careful dissection of the arteries and veins in the corresponding mesentery did not disclose thrombi in either system. Whether she had had an intussusception or volvulus that had reduced itself or whether we failed to find the embolus, I cannot say with certainty.

There were various other coincidental findings that a woman of seventy-nine might have, including a gall bladder full of stones and a completely stenosed cervical canal, which in a younger woman would have led to pyometrium and other complications.

DR BLAND Why do you think the thrombi formed in the right ventricle?

DR MALLORY I cannot say. There was no evidence of infarct beneath the areas of thrombosis.

DR BLAND She was not fibrillating. The heart was not large.

DR BENJAMIN CASTLEMAN Could the thrombi have come from the leg veins — emboli that had become arrested in the ventricle and become attached?

DR MALLORY I suppose it is conceivable. I have never seen it happen.

DR BLAND Do you recall what the left base looked like? Was that infarcted?

DR MALLORY Infarcted — there was no fluid on either side.

DR BLAND The X-ray Department is to be congratulated on pointing out the finding of an obstructed pulmonary artery, and from films taken with a portable machine.

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## ONE HUNDRED AND SIXTY-SEVENTH ANNIVERSARY

The recent annual meeting of the Massachusetts Medical Society, making its one hundred and sixty seventh anniversary, was one of the best attended and most successful meetings in the history of the Society. The number of registrants totaled 2436. At the Council meeting, held on May 24, a number of currently important subjects were discussed in addition to the routine acceptance of committee reports.

The matter of better emergency medical service, which has caused mild agitation in recent months, was referred to the district societies for consideration and solution. A supplementary report of the Committee on Finance called attention to the new classification into which the Society has been placed by the Treasury Department and the Massachusetts Division of Taxation. This classification so modifies the status of the Society as a charitable, benevolent and educational organization as to render it liable for old-age assistance and unemployment levies.

The subject of the physician's unsatisfactory situation regarding procurement and assignment during the recent war was brought up, and the present bill before Congress relative to the drafting of physicians in case of a national emergency was condemned.

The following officers were elected for the year 1948-1949: president, Daniel B. Reardon, president-elect, Arthur W. Allen, vice-president, Donald Munro, secretary, H. Quimby Gallupe, treasurer, Eliot Hubbard, Jr., assistant treasurer, Norman A. Welch, orator, Charles Sidney Burwell.

Dr. Reardon, in acknowledging his introduction as incoming president, emphasized the duty of the Society to explore the roll of physicians in the Commonwealth who are not now fellows, that those who are eligible for fellowship or who can become eligible, may be encouraged to achieve that status. Dr. Reardon's address is printed on the following pages of the *Journal*.

At the annual meeting of the Society on May 25 certain amendments to the by-laws were accepted, the chief of which changed the secretaryship of the Society to a full-time position. The President then reported on "the state of the Society," members of the Society fifty years in practice were introduced, and honorary fellowship was conferred upon Sir Reginald Watson-Jones, of London, orthopedic surgeon to H. M. George VI and surgeon-in-chief of the Royal Air Force. The annual oration, which has already been published in the *Journal* of May 27, was delivered by Dr. Allen S. Johnson, of Springfield.

The Shattuck Lecture, appearing elsewhere in this issue of the *Journal*, was delivered on the evening of May 25 by Dr. C. Stuart Welch, professor of surgery at Tufts College Medical School.

The newly formed woman's auxiliary of the Society held its organizational meeting on May 26, at which time the following officers were elected: president, Mrs. Leighton F. Johnson, of Wellesley Hills, vice-president, Mrs. Charles C. Ayers, of Worcester, secretary, Mrs. John F. Conlin, of Boston, treasurer, Mrs. Leo G. Rondeau, of Boston.

At the annual dinner on May 26, Mary Ellen Chase, Ph.D., Professor of English Language and Literature at Smith College, addressed a capacity audience on the subject of "The Country Doctor on the Maine Coast."

The scientific papers, as usual, were of high caliber, and the sessions were well attended. The scientific and technical exhibits aroused interest, and great credit is due to the Committee on Arrangements and the indefatigable executive secretary.

# MASSACHUSETTS MEDICAL SOCIETY

## PRESIDENTIAL ADDRESS

I find it difficult to express the sentiments that are mine as I assume the chair of president of this ancient brotherhood. Surely among thousands of the professional societies of our nation it is unique, for it combines the traditions of long years with policies dedicated to the forward march of medicine in this well loved Commonwealth of ours. No one who has spent nearly fifty years as student and practitioner in the field that binds all here together can take this chair without strong pride that his brothers have placed their faith in him and that he may serve honorably and well in the footsteps of all those men who have preceded him, from Edward Augustus Holyoke in the beginning to our own Edward Parsons Bagg today. To Dr. Bagg particularly go my thanks for his kindness and help to me during the period of education that has been mine as president-elect. To the chairmen of all our working committees who have extended invitations to me to attend their many meetings during the past twelve months, I also express my gratitude. And to yourselves, representing as you do our large and distinguished fellowship, I convey my heartfelt appreciation for the confidence reposed in me that my election to the presidency indicates. I promise you I shall not fail you. The honor done me is freighted with responsibility. That I recognize and accept.

The careful discharge of the duties of the office of president, however, depends in large measure on the co-operation extended by those of our members who serve upon our numerous committees. Committee work such as ours must necessarily be calls for much corporate dedication of time and effort. The only thanks in return for this sacrifice is the knowledge of our committee members that by their labors they have advanced the profession in those avenues in which their work lies, but *that* is reward sufficient to most. I have been greatly impressed, during this year of apprenticeship just past, to see the remarkable fidelity of the men on a number of our more important committees, and I can but commend their example to those who enter upon such work for the first time this year. To the incoming President-Elect I pledge my assistance that he may arrive at his post as President next year as liberally educated as I believe I am today in the many and various endeavors that we are carrying forward.

I propose also to explore new territories in which the Society may prove its worth to the profession. We have some 2000 physicians in the Commonwealth who, for one reason or another, are not numbered in our membership. The continuance of our strength depends in large measure on our numbers. Every properly qualified physician should be with us. For

those not with us an analysis should be undertaken to determine whether the fault be theirs or ours. I have the strong opinion that the coming years are going to find us under various forms of attack as a profession. We must meet such onslaughts with a major force, that when we speak we shall speak with the authority that the weight of numbers conveys. We should do all in our power to assist those men in practice outside our ranks who are substandard by education or experience. For them as well as for our members, the committees on the Postgraduate Assembly and Postgraduate Medical Education under Drs. Parkins and Ohler have done much. I state the hope that we may do even more.

The issuance of membership cards duly certified to members in good standing is a matter that might receive some consideration by the Council, in the light of practice elsewhere among professional societies, and also for the purpose of identification, which seems to become important in some quarters from time to time.

Another question that has been brought to my attention by some of our members has to do with the fundamental well-being of many of the members. I judge that I am right in saying that the great majority of Massachusetts physicians are not on salary. They, therefore, in common with all the self-employed do not in any way share in the retirement and old-age benefits extended to many nonprofessional executives.

You are aware of cases in which old age in a doctor has brought financial distress. Too often, improper husbanding of capital and income during the earning years has led to a standard of living that the physician finds it impossible to maintain in his advanced years. Present high prices serve but to emphasize the dilemma that confronts many of our members. I have had occasion during the past year to look into the question of some system of retirement benefits for the members of the Society, and I understand that several of the local bar associations are in the process of similar investigation. Two facts are clear at this moment. One is that present law on our statute books prevents us from moving forward on any such program were it agreeable to the Society. If, after due consideration, it appears wise to go further I should suggest that in company with other like-minded groups we might move to seek amendatory legislation opening the way for enjoyment by our members on a contributory basis of the same program that has proved itself a boon to many other groups. A second fact of importance here is that the Congress of the United States has under advisement an extension of the Social Security program to the self-employed and to the professions on a voluntary scale. National action might well be the

answer to the problem I have just set out. My belief, is, however, that the appointment of a committee by your authority, to go over this entire matter might be a wise move.

These, then, are a few of the thoughts on my mind at our meeting today. As I said at the beginning, my entry into the presidency of the Society caps for me a lifetime in the practice of the medical profession, and means more to me than anything I might ever have achieved. We are all inheritors from some very great men. Where else might one search in the world for the medical progress that has marked the history of this Commonwealth, small in area and large in influence, in the last century and a half? It is the task of all of us to carry the torch as high as our predecessors placed it. I recall that Arthur Balfour, writing of the work of the First Harvard Unit (to which I had the good fortune to be attached) during World War I, said, "They have added luster even to the fame of Harvard." May it be said of us working together during the next twelve months "And they have added luster even to the fame of the Massachusetts Medical Society." With that high goal and in that spirit, may we enter upon our respective duties in the sure knowledge that we will not fail!

DANIEL B. REARDON

## DEATHS

**COLE**—William G. Cole, M.D., of Pittsfield, died on April 16. He was in his forty-seventh year.

Dr. Cole received his degree from Columbia University College of Physicians and Surgeons in 1928. He was a member of the American College of Radiology and a fellow of the American Medical Association. He was roentgenologist in chief at House of Mercy Hospital.

His widow and a daughter survive.

**CONNOR**—George J. Connor, M.D., of Haverhill died on April 19. He was in his sixty-second year.

Dr. Connor received his degree from Maryland Medical College in 1909. He was a counselor of the Essex North District Medical Society and chairman of the Committee on Public Relations, chairman of the Haverhill Board of Health and a fellow of the American Medical Association.

His widow survives.

**GILBERT**—Maurice A. Gilbert, M.D., of Chelsea died on January 18. He was in his sixty-first year.

Dr. Gilbert received his degree from Tufts College Medical School in 1914. He was a member of the staffs of the Chelsea Memorial Hospital and the Whidden Memorial Hospital in Everett and was a fellow of the American Medical Association.

His widow, his mother, a brother and two sisters survive.

**MASON**—Nathaniel R. Mason, M.D., formerly of Marblehead, died on May 6. He was in his seventy-third year.

Dr. Mason received his degree from Harvard Medical School in 1901. He was a fellow of the American College of Surgeons and a retired member of the Massachusetts Medical Society.

His widow survives.

**MCCREADY**—Leo T. McCready, M.D., of Jamaica Plain died on May 5. He was in his sixty-ninth year.

Dr. McCready received his degree from Tufts College Medical School in 1906. During World War II he was examining physician for the local Selective Service board.

Four sons and four daughters survive.

## MISCELLANY

### BOSTON MEDICAL HISTORY CLUB

The annual meeting of the Boston Medical History Club was held at the Boston Medical Library on May 18, 1948. The following officers were elected for the ensuing year: president, Dr. Reginald Fitz; vice president, Dr. John Fallon; and secretary-treasurer, Mr. James F. Ballard. Drs. Benjamin Spector, Madeline R. Brown, Harold Bowditch and Paul D. White and Mr. James F. Ballard were elected to the Council.

The principal speaker of the evening was Dr. Benjamin Spector, professor of anatomy and professor of the history of medicine, Tufts College Medical School. Dr. Spector discussed the work of the early pioneers in medicine in Italy from the time of the School of Salerno (about 1200) to Camillo Golgi (1844-1926), and its influence upon present-day medicine. The speaker pointed out the cosmopolitan character of the Salernum School and its work in anatomy, surgery, and medicine. He mentioned in particular the study of occupational diseases by Bernardino Ramazzini (1633-1714) of metabolism by Sanctus (1561-1636) and of epidemics by Fracastoro (1483-1553); the development of the theory of spontaneous generation by Francesco Redi, Lazzaro Spallanzani and Agostino Bassi (1626 to 1656); the early use of the microscope by Galileo (1564-1642) and Amici (1786-1863); the humanist anatomists, physicians and artists, Leonico de' Vio and Vesalius; and finally the work of the Nobel Prize winner Golgi on the nervous system.

Mr. James F. Ballard of the Boston Medical Library spoke briefly on three notable medical figures of the Italian Renaissance—Marsilio Ficino, Philippus Beroaldus and Hieronymus Cardanus—and demonstrated their works many of which were first editions.

In connection with Dr. Spector's address, selected works of the physicians discussed, as well as thirteenth century manuscripts of the Salernum period were shown.

## BOOK REVIEWS

*Nicolaus Pol Doctor 1494*. By Max H. Fisch, Ph.D. With a critical text of his *Gusac tract* edited with a translation by Dorothy M. Schullian, Ph.D. New York: Published for The Cleveland Medical Library Association by Herbert Reichner, 1947. 87 pp.

Nicolaus Pol, physician lived in the latter part of the fifteenth century and the early part of the sixteenth century. The date of his birth is unknown but it is assumed to have been about 1470 or a little earlier. He died in 1532. He was one of a group of famous physicians who collected comparatively large libraries for the period. Among those may be mentioned Ulrich Ellenbog, Hieronymus Munzer and Hartmann Schedel the author of the famous Nuremberg Chronicle.

E. P. Goldschmidt in 1938 published a monograph on the library of Hieronymus Munzer in which 185 titles are identified. (All the books and manuscripts were dated before the fifteenth century, except for two volumes printed in 1501 and 1503; this is easily understood since Munzer died in 1508.) Max Fisch in this study of the library of Nicolaus Pol has identified 467 titles. However, 186 were printed in the sixteenth century. The libraries of these physicians were generally scholarly in character, the number of strictly medical books being comparatively few except that of Pol. In which the number of medical and scientific incunabula number a hundred and thirty three, or 53 per cent of the total incunabula, or the basis of the Klebs census. Goldschmidt prefaces his description of the Munzer library with a scholarly life of Munzer. Likewise Fisch begins his book with a short biography of Pol. This is followed by a critical analysis of Pol's only published work, his tract on the gusac cure of syphilis, supplemented by a critical text edited from the manuscript in the Army Medical Library (about 1519) and the Venice edition (1535) with a page-by-page translation by Dorothy Schullian. The remainder of the volume is devoted to a description of the Pol books in the library of the Cleveland Medical Library Association and in the Historical Library of the Yale Medical School and to a list of identified Pol books. The Cleveland collection consists of thirty-eight titles of the fifteenth and two of the sixteenth century. Of the incunabula are medical, whereas the re-

(1935) and the old *B N A* (1895) nomenclatures. There is an excellent comprehensive index of subjects. The book is written for the student and practitioner and should prove useful to all German-reading physicians. It is recommended for all large medical libraries.

*Pediatric Progress Therapeutics of infancy and childhood*. Edited by Harry R. Litchfield, M.D., consultant in pediatrics, Rockaway Beach Hospital, New York City, attending pediatrician, Beth El Hospital, Brooklyn Women's Hospital and Brooklyn Thoracic Hospital, and chief in pediatrics, East New York Dispensary, Brooklyn, New York, and Leon H. Dembo, M.D., director of pediatrics, St. Ann's Hospital, visiting physician, St. Luke's Hospital, and consultant in pediatrics, Polyclinic Hospital, Cleveland, Ohio. 8°, cloth, 525 pp., with 47 illustrations. Philadelphia: F. A. Davis Company, 1948. \$8.00.

This annual, first published in 1947, is intended to supplement the comprehensive treatise, *Therapeutics of Infancy and Childhood*, published in 1947. The volume contains material of practical application and importance. It is the joint work of nineteen specialists. The following subjects are of special interest: use of the grid technic as a guide in the treatment of diseases causing growth failure in children, modern therapy of the dysenteries and salmonella infections, the use of thiourea drugs in hyperthyroidism, the Coburn treatment of rheumatic fever, the clinical use of normal human serum (gamma globulin), and antibiotic therapy. There is new material on viral hepatitis, toxoplasmosis, virus pneumonia, folic acid in anemia, therapy of allergic diseases and the Rh factor in therapeutics. A chapter on hernias in infants and children concludes the volume. There is a good index. The publishing is excellent in every way. The serial is recommended for all medical libraries and should prove valuable to pediatricians.

*The Practice of Group Therapy*. S. R. Slavson, editor. With a foreword by Nolan D. C. Lewis, M.D., 8°, cloth, 271 pp. New York: International Universities Press, 1947. \$5.00.

This book describes specifically the application of various types of group therapy to emotionally disturbed, socially maladjusted and mentally diseased patients as they are met with in the practice of psychiatry and psychotherapy. The work comprises thirteen papers by various authorities, and most of the chapters are based on papers presented at the conferences of the American Group Therapy Association held in 1945-1947. The text is divided into three parts: general principles, activity group therapy, and interview group therapy, sometimes called discussion therapy. A chapter on didactic group psychotherapy with psychotic patients is also included. Four chapters dealing with the actual treatment of cases are valuable in demonstrating the process employed in group therapy. The volume is well published in every way and should be in all psychiatric collections.

*Ulcer: The primary cause of gastric and duodenal ulcer. Diagnosis, medical and surgical treatment, prevention*. By Donald Cook, M.D., Chicago. 8°, cloth, 187 pp., with 27 illustrations. Chicago: Medical Center Foundation and Fund, 1946. \$6.00.

This short monograph discusses the various aspects of gastroduodenal ulcers.

*A Primer on Cardiology*. By George E. Burch, M.D., associate professor of medicine, Tulane University School of Medicine, senior visiting physician, Charity Hospital, consultant in cardiovascular diseases, Ochsner Clinic, and visiting physician, Touro Infirmary, New Orleans, and Paul Reaser, M.D., instructor in medicine, Tulane University School of Medicine, and assistant visiting physician, Charity Hospital, New Orleans. 8°, cloth, 272 pp., with 203 illustrations. Philadelphia: Lea and Febiger, 1947. \$4.50.

This manual, which is written primarily for the beginner in cardiology, emphasizes diagnosis. There is a chapter on the common heart diseases. An appendix includes the nomenclature and classification of heart disease of the New York and American Heart associations, cardiac measurements, diets and statistics of heart disease. The material is well arranged, and the text well written.

*Gynecological and Obstetrical Urology*. By Houston S. Everett, A.M., M.D., associate professor of gynecology, Johns Hopkins University School of Medicine, and associate in gynecology, University of Maryland School of Medicine, gynecologist and gynecologist in charge of the Cystoscopic Clinic, Johns Hopkins Hospital, visiting gynecologist, Church Home and Hospital, Hospital for the Women of Maryland and Union Memorial Hospital. Second edition. 8°, cloth, 539 pp. Baltimore: Williams and Wilkins Company, 1947. \$6.00.

In this second edition of a standard textbook, which was out of print a year and a half after publication of the first edition, the author has endeavored to bring the text and bibliographies up to date, but has not made any major additions to his text. A section on indirect cystoscopy has been added to the chapter on cystoscopy. The section on primary neoplasms of the bladder has been revised and a description of the Aldridge operation for stress incontinence has been added to the chapter on incontinence of urine. A good index concludes the volume. The book is well published in every way, and is recommended for all medical libraries.

## NOTICES

### ANNOUNCEMENTS

Dr. Daniel H. Hindman announces the removal of his office to 1093 Beacon Street, Brookline.

Dr. Samuel B. Kirkwood announces the removal of his office for the practice of obstetrics and gynecology to 1180 Beacon Street, Brookline.

Dr. Lucile Williamson announces the removal of her office from 412 Beacon Street to 399 Beacon Street, Boston, for the practice of pediatrics and allergic diseases.

### HARVARD SEMINAR ON HEALTH EDUCATION

The Massachusetts Department of Public Health, in cooperation with the Harvard Summer School of Arts and Sciences and of Education, is offering a four-week graduate seminar in health education from June 28 to July 23. The course is intended for school administrators, teachers of nutrition, social studies, health and physical education and agency personnel concerned with school health problems.

Mary E. Spencer, Ph.D., chief co-ordinator of public health education, Massachusetts Department of Public Health, has been appointed a member of the Harvard Summer School faculty to conduct the course. Visiting consultants will include physicians from the Massachusetts Department of Public Health, members of the staff of the Harvard School of Public Health and such outstanding authorities as John F. Conlin, M.D., M.P.H., director of medical information and education, Massachusetts Medical Society, C. Mayhew Derryberry, Ph.D., chief, Office of Health Education, United States Public Health Service, Charles C. Wilson, M.D., professor of public health, Yale University School of Medicine, W. W. Bauer, M.D., director of health education, American Medical Association, and C. E. Turner, Dr. P.H., assistant to the president, National Foundation for Infantile Paralysis.

Information regarding the seminar may be obtained from the director of the Harvard Summer School of Arts and Sciences and of Education, 9 Wadsworth House, Cambridge, and from the Massachusetts Department of Public Health, Room 524, State House, Boston.

The course will accommodate thirty students.

### TUFTS MEDICAL ALUMNI ASSOCIATION

The Tufts Medical Alumni Association will hold a dinner meeting in Chicago on Wednesday, June 23, at the Windermere East Hotel, 56th Street and Hyde Park Boulevard, Chicago. Dr. Harry A. Olin, of Chicago, is local chairman, and Dr. John F. Conlin is the Boston chairman of this event.

(Notices concluded on page xi)

## NOTICES (Concluded from page 856)

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 17

## FRIDAY JUNE 18

9:00-10:00 a.m. Cardiospasm Dr Franz J Ingelfinger Joseph H. Pratt Diagnostic Hospital.

10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

## TUESDAY JUNE 22

12:15-1:15 p.m. Chlathrocytogenetological Conference Peter Bent Brigham Hospital

1:30-2:30 p.m. Pediatric Rounds. Burreham Memorial Hospital for Children, Massachusetts General Hospital.

## WEDNESDAY JUNE 23

9:00-10:00 a.m. Myelography Dr Samuel Blank, Joseph H. Pratt Diagnostic Hospital.

12:00 m. Clinicopathological Conference. (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

\*Open to the medical profession.

June 14-16, American Neurological Association. Page 582 issue of April 15

June 16-18, New England Health Institute. Page 754 issue of May 20

June 17-20 American College of Chest Physicians. Page 455 issue of March 25

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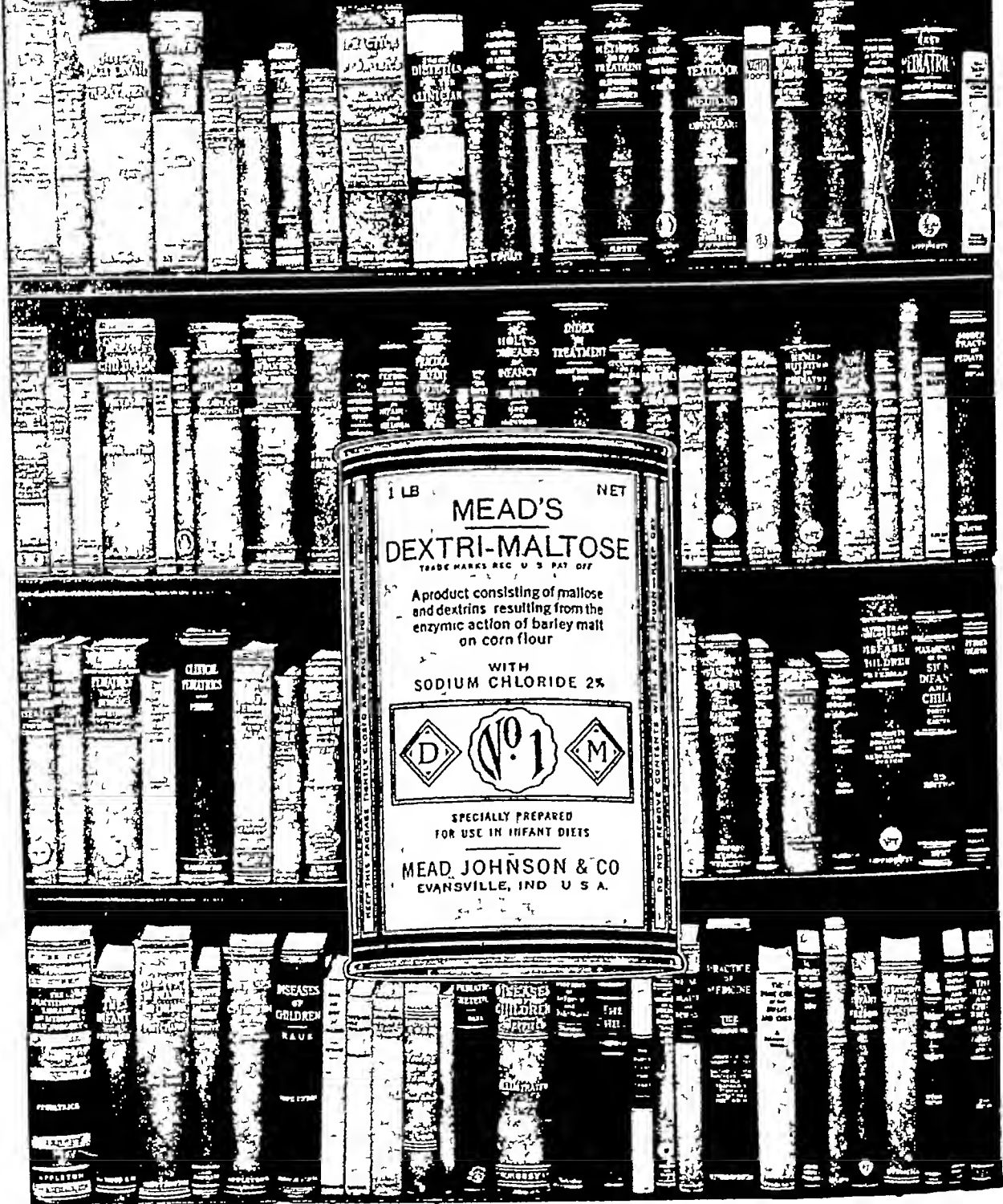
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## OSTEOARTHRITIS OF THE CERVICODORSAL SPINE (RADICULITIS) SIMULATING CORONARY-ARTERY DISEASE

### Clinical and Roentgenologic Findings

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BOSTON

IN a previous report, attention was called to the occurrence of attacks of severe substernal and precordial pain in radiculitis of the dorsal spine.<sup>1</sup> In this communication, the clinical and roentgenologic findings are analyzed in a group of 43 patients with this condition. Although it has been established that pain in the shoulder girdle and anterior portion of the chest are often due to postural strain and hypertrophic arthritis of the spine, certain clinical aspects, such as the character and severity of the attacks, the occurrence of respiratory symptoms and the significance of parasternal tenderness, require further study and emphasis. Furthermore, although a few authors have discussed the roentgenologic findings in cervical radiculitis, there are few or no statistical data on the changes in the dorsal spine. This information was considered particularly important because radicular pain is frequently confused with that of coronary-artery origin. In fact, 23 of these 43 patients were thought to have coronary-artery disease or thrombosis before the diagnosis of radiculitis was established.

### CRITERIA FOR DIAGNOSIS

The diagnosis of radiculitis in each case was based on the presence of at least two of the following criteria: symptoms with definite radicular characteristics; reproduction of attacks by pressure over the spine, and prompt response to orthopedic therapy. The pain in the majority of cases presented the cardinal features of radiculitis—that is, attacks in bed at night, precipitation or aggravation of pain with changes in bodily position, as in stooping or turning in bed, and production or aggravation of pain by such acts as coughing, sneezing or straining at stool. Pain in the anterior portion of the chest was reproduced in 19 patients

during one or more examinations by pressure over the dorsal spine, and 9 additional patients experienced definite relief on hyperextension of the spine. The response to traction and other orthopedic measures was sufficiently striking in 28 cases to be of diagnostic significance. The history, physical examination and repeated electrocardiograms with six standard chest leads showed no evidence of coronary-artery disease in 37 cases. Six additional patients in the series had coexisting heart disease. These cases were included because the clinical evidence of radiculitis was incontrovertible.

### CLINICAL ASPECTS

Tables 1 and 2 summarize the clinical observations and roentgenologic findings in the cervical and dorsal spine in this group of 43 cases, which consisted of 32 male and 11 female patients, with an average age of fifty-two years. Although the patients were selected primarily on the basis of chest pain due to radiculitis of the dorsal spine, they were also studied for manifestations of cervical origin, such as shoulder-girdle pain, suboccipital headache, vertigo and spasm and tenderness of the posterior cervical muscles. Each patient was observed carefully over a period of weeks to months and, in some cases, years before the diagnosis of radiculitis was conclusively established.

The spinal nerves, composed of anterior and posterior roots, join just within the intervertebral foramina. Pain arising from irritation of the sensory roots is felt subjectively in or referred to the corresponding dermatomes represented by these nerves. The close similarity of the symptoms in radiculitis and coronary-artery disease is explained by the fact that the pain in both is dependent, at least in part, on afferent impulses from the same skin or muscle structures.<sup>2, 3</sup>

Phillips,<sup>4</sup> in 1927, called attention to the importance of examining the spine in thoracic and abdominal pain and showed that pain of this origin

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TABLE 1 *Clinical Findings in the Cervical and Dorsal Spine*

CASE No	AGE	SEX	DURATION OF ILLNESS	No OF ATTACKS	DORSAL SPINE										
					LOCATION OF CHEST PAIN	RADIATION OF PAIN	PAIN AT NIGHT	PAIN AFTER SITTING	PAIN ON BENDING, ETC	PAIN ON COUGHING, ETC.	RELIEF ON CHANGE IN POSITION	RESPIRATORY DISTRESS	DORSAL TENDERNESS	COSTO-CHONDRAL TENDERNESS	REPRODUCTION OF ATTACKS
1	50	F	2	Many	Substernal, precordial and inter-seapular	Neck	Present	Present	Present	Present	Present	Present	Present	Present	Present
2	63	M	5	Many	Substernal and precordial	Shoulder girdle and neck	Present	Present	Present	Absent	Present	Present	Present	Present	Absent
3	46	F	—*	Many	Substernal and precordial	Neck and jaw	Present	Present	Present	Absent	Present	Absent	Present	Present	Present
4	74	M	7	Many	Substernal	Shoulder girdle	Present	Present	Present	Absent	Present	Present	Absent	Present	Present
5	68	M	1/6	Many	Substernal and precordial	Neck	Present	Present	Absent	Absent	Present	Present	Absent	Present	Absent
6	53	M	1	Many	Precordial and axillary	Shoulder girdle	Present	Present	Present	Absent	Present	Absent	Present	Present	Absent
7	59	M	5	Many	Substernal and precordial	Shoulder girdle	Present	Absent	Absent	Absent	Present	Present	Absent	Present	Absent
8	73	F	1	Many	Substernal and precordial	Shoulder girdle	Present	Present	Absent	Absent	Absent	Present	Present	Present	Present
9	37	M	1	3	Precordial	Absent	Present	Present	Present	Present	Present	Present	Present	Absent	Present
10	49	M	1/6	Many	Substernal	Shoulder girdle	Present	Present	Absent	Absent	Present	Present	Present	Present	Absent
11	40	M	6	8	Substernal	Shoulder girdle and jaw	Present	Present	Present	Absent	Present	Absent	Present	—	Absent
12	54	M	18	Many	Substernal	Absent	Absent	Present	Present	Absent	Present	Present	Absent	Absent	Absent
13	57	M	3	Many	Substernal precordial and inter-seapular	Absent	Present	Absent	Present	Absent	Present	Present	Present	Present	Present
14	52	M	1/4	Many	Substernal and neck	Shoulder girdle	—	—	Present	Present	Present	—	Present	Present	Present
15	50	M	1	Many	Precordial	Interseapular and shoulder girdle	Absent	Present	Present	Absent	Present	Present	Present	Present	Present
16	64	M	5	Many	Precordial	Absent	Present	Present	—	—	—	Present	—	Present	—
17	50	M	1/10	Many	Substernal	Neck	Present	Present	Present	Absent	Present	Absent	Absent	Present	Absent
18	52	M	1/10	Many	Substernal	Absent	Absent	Absent	Present	—	Present	—	—	—	Absent
19	35	M	1 1/2	Many	Precordial and inter-seapular	Shoulder girdle and neck	Present	Present	Present	Absent	Present	Absent	Absent	Present	Present
20	62	M	2 1/2	Many	Substernal	Shoulder girdle, neck and jaw	Present	Present	Present	Present	Present	Absent	Present	—	Present
21	57	M	1/3	Many	Substernal	Shoulder girdle	Present	Present	Absent	Present	Present	Absent	Present	Present	Present
22	48	M	1	Many	Substernal	Shoulder girdle	Present	Present	Absent	Absent	Present	Absent	Present	Present	Present
23	52	F	2 1/2	Many	Precordial	Shoulder girdle	Present	Present	Absent	Absent	Absent	Absent	Present	Present	Absent
24	42	M	—*	—	Substernal	Shoulder girdle	Absent	Absent	Absent	Absent	Present	Absent	Present	Present	Absent
25	61	F	5	Many	Substernal and precordial	Shoulder girdle	Absent	Present	Absent	Absent	—	—	Present	Present	—
26	46	M	9	Many	Substernal	Absent	Present	Present	Absent	Absent	Present	Absent	Absent	Present	Absent
27	25	F	1/6	Many	Substernal	Absent	Present	Absent	Present	Present	Present	Present	Present	Present	Absent
28	37	M	1/10	Many	Substernal, precordial and inter-seapular	—	Present	Present	Present	Present	—	Present	Present	—	Present
29	56	F	1/2	Many	Precordial and axillary	Shoulder girdle and axilla	Present	Present	Present	Absent	Present	—	Present	—	Absent
30	58	M	1/10	Many	Substernal	Shoulder girdle	Absent	Present	Absent	Present	Present	Absent	Present	Present	Present
31	66	M	5	3	—	Absent	Absent	Present	—	Absent	Present	Absent	Present	—	Present
32	54	F	3	Many	Substernal and precordial	Substernal neck and jaw	Present	Present	Present	Present	Present	Absent	—	Present	Present
33	58	F	3	Many	Substernal, precordial and inter-seapular	Neck	Present	Present	Present	Present	—	Absent	Present	—	Present
34	60	M	1	Many	Substernal	Shoulder girdle	Present	Absent	Present	Absent	Present	Present	Absent	Absent	Absent
35	44	M	1/2	Many	Substernal	Neck and axilla	Present	Present	Absent	Absent	Absent	Present	Present	Present	Absent
36	50	F	1/16	Many	Substernal	Shoulder girdle	Present	Present	Absent	Absent	Present	Absent	Absent	Present	Present
37	53	F	5	Many	Substernal	Neck and axilla	Absent	Absent	Present	Absent	—	Absent	Present	Present	Present
38	53	M	2	Many	Substernal	Neck	Present	Present	Present	Absent	Present	Absent	Absent	Absent	Absent
39	46	M	—*	Many	Substernal	Shoulder girdle	Present	Absent	Absent	Absent	—	Absent	—	Present	Absent
40	62	M	1/2	4	Absent	—	Present	—	—	—	Present	Present	Present	Present	—
41	47	M	2	Many	Precordial and inter-seapular	Shoulder girdle	—	Present	—	—	—	Present	Absent	Absent	Absent
42	63	M	1/10	Many	Substernal	Shoulder girdle	Absent	Absent	Absent	Absent	Present	Present	Present	Present	Absent
43	51	M	1/4	Many	Precordial	Shoulder girdle	—	Present	Present	—	Present	Absent	Absent	Present	Absent

\*Disease present for days in cases indicated.

TABLE 1 (Continued)

CASE NO.	SHOULDER GIRDLE PAIN	SUN OCCIPITAL HEADACHE	VERTIGO	POSTERIOR CERVICAL MUSCLE SPASM	POSTERIOR CERVICAL MUSCLE TENDERNESS	LIMITED NECK ROTATION	PAIN IN LOWER BACK	ELECTRO-CARDIO-GRAM TAKEN	HYPERTENSION	CORONARY ARTERY DISEASE OR CONGENITAL HEART FAILURE	THERAPEUTIC RESPONSE
1	Present	Present	Present	Present	Present	Present	Present	No	Present	Absent	Yes
2	Present	Absent	Absent	Present	Absent	Present	Present	No	Absent	Present	Yes
3	Present	Present	Present	Present	Present	Present	Absent	Yes	Absent	Present	Yes
4	Present	Present	—	Present	Present	Present	Present	Yes	Absent	Present	Yes
5	Present	Present	Present	Present	Present	Present	Present	No	Present	Absent	Yes
6	Present	Absent	Present	Present	Present	Present	Absent	No	Absent	Absent	Yes
7	Present	Absent	Present	Present	Present	Present	Absent	Yes	Absent	Present	Yes
8	Present	Present	Absent	Present	Present	Present	Present	No	Absent	Absent	—
9	—	Absent	Absent	Present	Present	Present	Absent	No	Absent	Absent	Yes
10	Present	Absent	Absent	Present	Present	Present	Absent	No	Absent	Absent	No
11	—	Absent	Absent	Present	Present	Present	Absent	No	Absent	Absent	No
12	Absent	Absent	Present	Present	Present	Present	Present	No	Absent	Absent	Yes
13	Absent	Absent	Absent	Present	Present	Present	Absent	Yes	Absent	Present	Yes
14	—	Present	—	—	—	—	—	No	Absent	Absent	Yes
15	Present	Present	Present	Absent	Absent	Present	Present	No	Absent	Absent	—
16	—	Absent	Present	Present	Present	Present	Present	No	Absent	Absent	—
17	—	Absent	Present	Present	Present	Present	Present	No	Absent	Absent	Yes
18	Present	Present	Present	Present	Present	Present	Present	No	Absent	Absent	—
19	Present	Present	Present	Present	Present	Present	Present	No	Absent	Absent	Yes
20	Present	Present	Present	Present	Present	Present	Absent	No	Absent	Absent	Yes
21	Absent	Absent	Present	Present	Present	Present	Present	No	Absent	Absent	—
22	Present	Absent	Absent	Present	Present	Present	Absent	No	Absent	Absent	—
23	Absent	Present	Present	Present	Present	Present	Absent	No	Absent	Absent	Yes
24	Present	Absent	Absent	Present	Present	Present	Present	No	Absent	Absent	Yes
25	Present	—	—	—	—	—	Present	No	Absent	Absent	—
26	Absent	Absent	Present	Present	Present	Present	Present	No	Absent	Absent	Yes
27	Present	Absent	Present	Present	Absent	Present	Present	No	Absent	Absent	Yes
28	—	Absent	Absent	Present	Present	Present	—	No	Absent	Absent	Yes
29	—	—	—	—	—	—	Present	No	Present	Absent	—
30	—	Present	Absent	Present	Present	Present	Present	No	Absent	Absent	Yes
31	Present	Present	Present	Present	Present	Present	—	No	Absent	Absent	Yes
32	—	Absent	Absent	Present	Present	Present	Present	No	Absent	Absent	Yes
33	—	Present	Present	Present	Present	Present	Absent	No	Present	Absent	—
34	Present	Present	Present	—	—	—	Present	Yes	Absent	Absent	Yes
35	Absent	Absent	Absent	Present	Present	Present	Absent	No	Absent	Absent	Yes
36	Present	Absent	Present	Present	Present	Present	Absent	No	Absent	Absent	Yes
37	—	Absent	Absent	Absent	Absent	Absent	Absent	No	Absent	Absent	—
38	—	—	Present	Absent	Absent	Absent	Absent	No	Present	Absent	—
39	Present	Absent	Absent	Present	Present	Present	Absent	No	Absent	Present	Yes
40	—	—	Present	Present	Present	Present	—	No	Absent	Absent	Yes
41	Present	Absent	Absent	Present	Present	Present	Absent	No	Absent	Absent	—
42	Present	Absent	Absent	Present	Present	Present	Present	No	Absent	Absent	Yes
43	—	Present	Present	Present	Present	Present	Present	No	Absent	Absent	Yes

could be mistaken for angina pectoris and gall-bladder and kidney disease. In the following year, Gunther, Sampson and Kerr<sup>5-7</sup> analyzed the cases of 50 patients whose chief complaint was pain in the anterior portion of the chest, often bilateral. The symptoms in their cases were generally mild and did not suggest pain of coronary-artery origin. In 1934 Nachlas<sup>8</sup> described 3 cases with pain in the anterior portion of the chest due to osteoarthritis of the spine simulating angina pectoris and coronary-artery disease. Later, Hanflig<sup>9,10</sup> dis-

picture was that of coronary thrombosis without evidence of infarction such as a subsequent rise in temperature, leukocytosis or alteration in the electrocardiogram. A few patients also experienced pain in the interscapular and axillary regions.

The majority had attacks while in bed at night, a well recognized characteristic of radicular pain. Eaton<sup>16</sup> suggests that this is probably related to an actual elongation of the spinal column that results after the reclining position has been maintained for several hours. He showed by roentgen-

TABLE 2 X-ray Findings in the Cervical and Dorsal Spine

CASE No	NARROWING OF DISKS	ANTERIOR OSTEO-PHYTES	POSTERIOR OSTEO-PHYTES	DEGREE OF OSTEO-PHYTOSIS	CERVICAL SPINE OSTEO-ARTHRITIS OF INTER-VERTEBRAL JOINTS	KYPHOSIS OR LORDOSIS	SCOLIOSIS	STRAIGHTENING	OSTEO-POROSIS
1	4-7	3-7	4-7	Advanced	4-5	—	Left	—	Moderate
2	—	3-7	3-7	Advanced	3-7	—	Right	Present	Moderate
3	—	5-6	—	Slight	—	—	—	Present	—
4	6-7	3-7	4-7	Advanced	5-6	—	—	Present	Advanced
5	—	3-7	4-7	Advanced	—	—	Right	—	—
6	—	5-6	—	Slight	—	—	—	Prescot	—
7	—	4-5	—	Slight	—	—	—	Prescot	—
8	4-6	4-6	5-6	Moderate	—	—	Left	Present	—
9	—	5-6	—	Slight	—	—	—	—	Slight
10	4-5	4-6	—	Moderate	—	Posterior	Left	—	Slight
11	—	5-6	—	Slight	—	—	—	—	—
12	4-6	4-7	5-6	Advanced	—	—	Right	Prescot	—
13	4-5	3-7	3-7	Advanced	—	—	Right	—	Moderate
14	6-7	4-7	—	Slight	—	—	Left	—	Slight
15	—	4-6	—	Moderate	—	—	Left	—	Slight
16	—	3-6	4-5	Advanced	4-5	Anterior	Right	—	—
17	—	4-6	—	Slight	—	Anterior	Left	—	—
18	—	3-7	4-6	Advanced	3-7	—	Left	Prescot	Slight
19	—	—	—	—	—	—	—	—	—
20	5-7	4-7	5-6	Moderate	—	—	Right	Present	Moderate
21	—	4-6	5	Slight	—	—	Left	—	—
22	—	4-6	—	Moderate	—	—	Right	Present	—
23	5-6	4-5	—	Slight	5-6	—	—	Prescot	Moderate
24	—	5-6	—	Slight	—	—	Right	—	Slight
25	5-7	4-7	5-6	Moderate	—	—	—	Present	Slight
26	5-6	4-6	5-6	Slight	—	—	Left	—	—
27	—	—	—	—	—	—	Right	—	—
28	—	4-5	—	Slight	—	—	Left	Present	—
29	4-7	4-7	5-6	Advanced	—	—	Left	Present	Moderate
30	5-7	3-7	4-6	Advanced	5	Anterior	Left	—	—
31	5-7	4-7	4-7	Advanced	5-6	—	Left	Present	Moderate
32	—	—	—	—	—	—	—	—	—
33	5-7	3-7	4-7	Advanced	—	—	Left	Present	Moderate
34	4-7	4-7	5-6	Advanced	5-6	—	Left	Prescot	Moderate
35	—	4-5	—	Slight	—	—	Right	Present	Slight
36	—	4-6	—	Slight	—	—	Left	Present	—
37	—	4-6	—	Slight	—	Anterior	Right	—	—
38	—	5-7	6-7	Moderate	—	—	—	Present	—
39	—	5-7	5-7	Moderate	4-7	—	Left	Present	Moderate
40	4-7	3-7	4-6	Moderate	5-6	Anterior	Left	—	Moderate
41	—	—	—	—	—	—	—	—	—
42	—	4-6	5-6	Moderate	—	—	Right	Present	Moderate
43	6-7	3-7	4-5	Moderate	—	—	Left	Present	Slight
Totals	18	39	23	39	11	6	31	23	22

cussed chest pain of radicular origin and stressed the diagnostic value of the response to orthopedic therapy. Further contributions to the subject were made by Oille,<sup>11</sup> Kelly,<sup>12</sup> Pawling<sup>13</sup> and Smith and Kountz.<sup>14</sup>

The most striking clinical finding in our patients was the occurrence of attacks of severe substernal or precordial pain, frequently radiating to the left upper extremity and occasionally to the neck and jaws and, in a few cases, accompanied by pallor and perspiration. The pain was almost always described as a pressure sensation, a heaviness or a vise-like constriction. In most cases the clinical

ologic studies before and after sleep that the height of the disks becomes significantly increased throughout the spine. In a few cases the attacks were almost exclusively nocturnal and, when bed rest was prescribed because of an erroneous diagnosis of coronary-artery disease, became more frequent and recurred during the day as well. One patient (Case 21) had eighteen severe attacks at night, but only three mild bouts during the day in a period of three months. Repeated attacks of substernal pain occurring mainly while the patient is recumbent should always raise the possibility of nerve-root origin.

A second cardinal feature of radicular pain is its relation to change in bodily position. The attacks in 33 patients had a close relation to prolonged sitting, particularly in a slouched position, and the chest pain was often relieved promptly on arising and walking about. Short bouts of pain occurred in 24 cases during such acts as bending, turning or getting out of bed. In prolonged coronary-artery pain, patients are commonly restless and not relieved in any position. In contrast several of these patients noted one or two positions that afforded

of walking, and a few were forced to slow down or stop, with some relief. In all but 3 cases, however, the attacks did not closely suggest the early stages of angina pectoris, seldom occurring exclusively in the course of walking. The pain was usually of longer duration, its onset often more gradual, and on resting the pain did not subside so quickly as that in angina pectoris. Most often there was a discrepancy between the number of attacks and the amount of walking or activity in general. For example, a patient might have many attacks in the

TABLE 2 (Continued)

CASE No.	NARROWING OF DISKS	ANTERIOR OSTEOPHYTES	POSTERIOR OSTEOPHYTES	DORSAL SPINE DEGREE OF OSTEO- PHYTOSIS	OSTEO- ARTHRITIS OF INTER- VERTEBRAL JOINTS	SCOLIOSIS	STERNOSIS	OSTEO- POROSIS
1	—	4-9	—	Moderate	—	Left	Present	Moderate
2	5-8	2-10	—	Advanced	—	Right	—	Moderate
3	—	6-8	—	Slight	—	Right	—	—
4	8-10	7-12	8-10	Advanced	—	Right	Present	Advanced
5	—	—	—	—	—	—	—	—
6	—	5-9	—	Advanced	—	Right	Present	Slight
7	—	7-8	—	Slight	—	Left	—	—
8	—	4-8	—	Slight	—	Right	Present	Slight
9	—	—	—	—	—	Left	—	Slight
10	—	—	—	—	—	Right	Present	Slight
11	—	6-8	—	Slight	—	—	—	—
12	—	6-10	—	Advanced	—	Right	Present	—
13	—	7-10	—	Moderate	—	Right	Present	—
14	—	7-8	—	Moderate	—	Left	Present	Slight
15	—	5-9	6-7	Advanced	—	—	Present	Moderate
16	6-7	6-12	—	Advanced	—	—	Present	Slight
17	5-6	5-9	—	Slight	—	Right	Present	—
18	—	4-8	—	Advanced	—	Left	Present	Slight
19	—	5-8	—	Slight	—	Left	—	—
20	—	6-9	—	Moderate	—	Left	—	Moderate
21	—	7-8	—	Slight	—	Right	—	—
22	—	6-8	—	Moderate	—	Right	Present	Moderate
23	—	4-5	—	Slight	—	—	Present	Slight
24	—	4-7	—	Moderate	—	Right	Present	Moderate
25	—	6-9	—	Moderate	—	Right	Present	Slight
26	2-8	1-5	—	Moderate	—	Left	Present	—
27	—	—	—	—	—	—	—	—
28	—	4-7	—	Slight	—	Right	Present	Slight
29	4-5	3-7	—	Moderate	—	—	—	Slight
30	—	6-10	7-8	Advanced	—	—	—	Slight
31	—	3-9	—	Advanced	—	—	—	Slight
32	—	5-6	—	Advanced	—	—	Present	Slight
33	—	4-9	—	Advanced	—	—	—	Moderate
34	—	—	—	—	—	—	—	—
35	—	6-9	—	Moderate	—	Right	Present	Slight
36	—	4-7	—	Moderate	—	Left	Present	Slight
37	—	6-9	—	Slight	—	—	—	—
38	—	6-12	—	Slight	—	Right	—	—
39	—	2-12	—	Moderate	—	Left	—	Moderate
40	—	2-12	—	Moderate	—	Right	—	Moderate
41	5-8	2-12	—	Moderate	—	Right	—	Moderate
42	—	2-10	4-7	Advanced	—	—	Present	Slight
43	—	2-12	—	Slight	—	—	—	—
Totals	7	39	4	39	—	30	23	30

relief. A physician (Case 11) found comfort in repeated attacks when he assumed a stooped position or lay supine. Most patients were relieved on "straightening up" or on hyperextending the spine. One patient (Case 1) obtained relief by sitting up in bed and exercising the arms. Getting out of bed and walking about usually terminated or relieved the symptoms within a few minutes. A third cardinal feature, precipitation or aggravation of pain after coughing, sneezing, sighing, deep breathing or straining at stool, was noted in 8 cases.

Twenty-two of these patients had attacks of substernal or precordial pain at some time in the course

course of slow walking and never on climbing many flights of stairs. The relief obtained on resting in several cases was found to be closely related to a tendency of the patient unconsciously to assume a more erect posture and even to hyperextend the spine. One patient, a twenty-four-year-old woman (Case 27), had attacks closely simulating angina pectoris. Under observation she was seen to assume an exaggerated kyphotic position while walking. With the onset of substernal pain, she slowed down, stopped and unconsciously corrected her posture. Attacks could not be reproduced in this case or in

others by exercise-tolerance tests under standard conditions

During acute episodes, many patients complained of a peculiar respiratory distress. Although the patients described this as "shortness of breath," careful inquiry revealed that the symptom consisted of an inability to take a deep breath. Without a carefully taken history, this might easily have been misinterpreted as a manifestation of heart disease.



FIGURE 1 Lateral View of Cervical Spine

*There are spurs about the anterior and posterior margins of the fifth and sixth cervical vertebrae, with narrowing of the disk between these vertebrae. There is straightening of the cervical spine, with practically complete absence of the normal lordosis. There is osteoarthritis of the posterior intervertebral articulation between the fifth and sixth cervical vertebrae with narrowing and irregularity of outline of this articulation.*

Nineteen patients presented this complaint. In association with the restriction of respiration, breathing was rapid and shallow in a few cases. As inability to take a deep breath is a common psychosomatic complaint, the patients were studied carefully to exclude this possibility. In several cases the respiratory symptoms could be provoked by pressure over the dorsal spine; in a few, the symptoms occurred in attacks as the presenting complaint with little or no chest pain, simulating attacks of cardiac asthma.<sup>16</sup> The exact mechanism is not clear, but it is probable that, as in cervical radiculitis, motor paths are involved causing muscle spasm with inhibition of respiration.

The most significant diagnostic sign in radiculitis of the dorsal spine is the production of substernal or precordial pain on the application of pressure in the region of the spinous processes. Twenty-six patients showed marked local tenderness over the dorsal vertebrae, and firm pressure caused attacks in 19 of these on one or more occasions. The reproduced pain did not always correspond with the segmental distribution of the corresponding root. In Case 1, for example, precordial pain radiating along the fourth dorsal root could be elicited by pressure from the second to the seventh dorsal vertebra. This may be explained by the fact that pressure applied over one region of the spine may be transmitted and cause nerve-root irritation at a point some distance away. The reproduced pain in most cases was similar in character and distribution to that noted in the spontaneous attacks. When the patient assumed a hyperextended position, the attacks were difficult to elicit. In a few cases chest pain was also caused by forceful flexion of the head. According to Eaton,<sup>16</sup> this act results in upward displacement of the spinal cord with tension on the nerve roots, which are fixed in the extradural tissues.

An important manifestation of dorsal-nerve-root irritation is tenderness in the region of the costochondral junctions, a sign noted by Phillips<sup>4</sup> in 1927. Such tenderness, often marked, was found in 29 of 34 patients. It frequently occurred on both sides of the sternum. In several cases there was exquisite tenderness from the second to the fifth junction, although the fourth left junction was the most frequent site. In some cases it persisted long after the chest pain had subsided. The parasternal tenderness could usually be reduced or eliminated by traction applied to the cervical spine.<sup>17</sup> A study of controls showed that it was found comparatively infrequently in normal subjects without radicular symptoms.

In addition to chest pain, many patients had other manifestations of cervical radiculitis. This is to be expected, for osteoarthritis of the spine is often generalized. Nachlas,<sup>8</sup> Hanflig,<sup>9,10</sup> and Kelly<sup>12</sup> have called attention to the frequency of shoulder-girdle pain, and Kelly has stressed the occurrence of two less commonly appreciated symptoms: vertigo and suboccipital headache. Twenty-one patients complained of attacks of vertigo, 15 of suboccipital headache, and one or both were present in 11 cases. There was a higher incidence of other signs of cervical involvement, with limitation of neck rotation, palpable muscle spasm and tenderness in 24 cases.

#### ROENTGENOLOGIC ASPECTS

Any factor that produces narrowing of the intervertebral foramina may be responsible for nerve-root irritation. Osteophytes about the margins of the vertebrae, thinning of the intervertebral

disks, osteoarthritis of the posterior spinal articulations (Fig 1) and postural changes may diminish the size of the foramina. Spurs along the anterior borders of the vertebrae are usually not of great clinical significance. Osteophytes occurring at the posterior aspects of the vertebral bodies, however, are a frequent cause of radicular pain, since they are apt to encroach on the neural foramina (Fig. 2). Statements in the literature indicate that liping may be found in approximately 50 per cent of patients over fifty years of age. In Garvin's<sup>13</sup> series of 2090 patients, all of whom were over fifty years of age, there were hypertrophic changes in the lumbar spine in 67 per cent of the men and 40 per cent of the women. Cottrell<sup>10</sup> reported an incidence of

The intervertebral disks may become flattened and narrowed with consequent diminution of the spaces between the vertebrae due to various factors. As a result of trauma, the nucleus pulposus may be



FIGURE 2. Oblique View of Cervical Spine

There are hypertrophic spurs at the posterior aspects of the sixth and seventh cervical vertebrae with osteoarthritic changes involving the posterior spinal articulation between these vertebrae. The encroachment on the intervertebral foramen is clearly shown.



FIGURE 3. Oblique View of Cervicodorsal Spine

There is spurring in the lower cervical and dorsal regions. The disk between the fifth and sixth cervical vertebrae is narrowed. The posterior spinal articulation shows osteoarthritic changes. There is definite encroachment on the intervertebral foramen at this level. The cervical spine is straightened. There is increased kyphosis in the upper dorsal region.

herniated, the disk ruptured, or the cartilage injured. With advancing age or in consequence of occupational trauma, the intervertebral disks lose their elasticity and become flattened. Since the disk receives its blood supply from the adjacent bone, disease of the vertebral body eventually interferes with the nutrition of the disk and causes flattening. The disks have no power of regeneration, hence the changes once established are permanent. A close correlation between thinning of the intervertebral disks and radicular symptoms has been demonstrated. Oppenheimer<sup>20</sup> in a series of 200 apparently healthy persons found only 22 (11 per cent) with disk narrowing. On the other hand, in a series of 312 unselected cases of narrowed intervertebral disks, he reported clinical signs or symptoms pointing to a lesion of the involved spinal roots in 267 (85 per cent). Our patients, selected primarily because of chest pain, showed narrowing

55 per cent in a study of the thoracic and lumbar regions in 80 unselected ward cases with an average age of fifty-two years. Only 28 (33 per cent) showed slight to advanced thoracic-spine involvement and some had evidence of radiculitis. In contrast, about 95 per cent of our patients with similar average age showed spurring in the dorsal or cervical regions. Posterior marginal spurs occurred in the cervical spine in 23 (53 per cent) and in the dorsal region in 4 cases.

of the disks in 18 cases (42 per cent) in the cervical spine and in 7 cases (17 per cent) in the dorsal region. Of the 18 patients with cervical-disk narrowing, 17 had clinical evidence of cervical radiculitis.

Osteoarthritis of the intervertebral joints, usually associated with disk thinning, frequently results in narrowing of the apophyseal joints. In the early

loses its mobility. The degree of decalcification may serve in a general manner as a guide to the degree or duration of the process. Osteoporosis occurred in the cervical spine in 22 of our cases. In 9 of these, the changes were slight, in 13, they were moderate or marked. In the dorsal spine, there were 30 patients with bone atrophy, 17 with slight, 12 with moderate, and 1 with advanced changes.

One of the striking roentgenologic findings in our series was the high incidence of abnormal curvatures. Scoliosis is generally associated with rotations or lists causing strain of the ligaments, intervertebral disks and articulations. Disk narrowings and marginal osteophytes may occur in long-standing scoliosis.<sup>22</sup> The cervical spine, which normally presents a moderate lordosis, may become straight, less frequently more lordotic and rarely



FIGURE 4 *Lateral View of Dorsal Spine*

*There are spur formations about the margins of the vertebrae with slight narrowings of the intervertebral disks. The dorsal kyphosis is increased, and there is osteoporosis of the bones of the spine.*

stage, there is a strain on the capsule and ligaments, with periarticular soft-tissue reactions that may cause compression of the nerve roots; later, eburnation and exostosis formation develop. Joint abnormalities were noted in 20 per cent of Oppenheimer's<sup>20</sup> cases with disk thinning. Hadley<sup>21</sup> states that changes in the posterior articulations of the spine produced pain due to nerve-root compression in 72 per cent of his cases. Roentgenologic evidence of osteoarthritis of the intervertebral joints was present in the cervical spine in 11 (26 per cent) of our 43 patients; it was not noted in the thoracic spine. Narrowing or irregularity of intervertebral foramina from combined causes, such as disk narrowing, posterior marginal osteophytes and arthritis of the intervertebral joints, was demonstrated in the cervical spine in 26 patients (39 per cent) and in the dorsal spine in 10.

Osteoporosis, which is a manifestation of bone atrophy, occurs when the spine becomes rigid or



FIGURE 5 *Anteroposterior Projection of Dorsal Spine.*

*There are large osteophytes about the margins of the bodies of the dorsal vertebrae, with scoliosis in the upper and middle dorsal regions.*

kyphotic, and in the dorsal region, increased kyphosis is the rule (Fig. 3 and 4). Figure 5 shows scoliosis in the upper and middle-dorsal regions. In our patients, the most frequent finding in the cervical spine was straightening, which occurred in 23 cases; exaggeration of the normal anterior curvature was found in 5 and kyphosis in 1, and there was scoliosis to the right in 12 and to the left in 19. In the dorsal spine, kyphosis was increased in 23 cases, scoliosis occurred in 30—19 to the right and 11 to the left.

## DISCUSSION

The literature on radiculitis due to disease or injury of the vertebrae and protrusions of the intervertebral disks is vast, it is meager, however, on the subject of hypertrophic arthritis and postural strain. In consequence, the general practitioner has had little opportunity to become familiar with the clinical manifestations of this condition, and it is not generally appreciated how commonly pain in the anterior portion of the chest may be of spinal origin. The data presented above demonstrate that this pain may occur in the form of severe attacks closely simulating coronary-artery disease.

Coronary-artery disease and hypertrophic arthritis of the spine with radicular symptoms may coexist in the same patient, for both are common with advancing age. Six patients with previous myocardial infarcts or congestive failure had, in addition, unmistakable attacks of radiculitis, and 1 of these developed repeated attacks after being in bed for many days. It was first believed that these episodes were of coronary-artery origin, but further study revealed incontrovertible evidence of nerve root irritation. Only after bed boards and traction treatment had been applied did the attacks subside.

It is known that hypertrophic arthritis of the spine may be present without producing clinical manifestations. However, evidence has accumulated to show that it causes symptoms more frequently than is generally appreciated. Prior to the development of bony changes, soft-tissue reactions occur, and these are not demonstrable roentgenographically. The roentgenologic demonstration of osteoarthritis may be of great aid in establishing the diagnosis of radiculitis. This is particularly true when the symptoms are of short duration, the attacks cannot be reproduced, or the radicular characteristics of the pain are not clear-cut.

One of the striking findings in our study was the high incidence of osteoarthritis of the cervical spine. This may be considered an index of coexisting dorsal-spine involvement. The studies of Shore<sup>23</sup> also indicated that the incidence of intervertebral-joint arthritis was generally similar in the cervical and dorsal regions in 100 cases that came to autopsy. He further noted that the greatest occurrence of spinal arthritis was in the lumbar region, and that involvement higher up bore a constant relation to the curves and weight-bearing lines of the spine. This supports the concept that postural deviations play a direct role in the pathogenesis of intervertebral-joint arthritis. Seventeen of our patients gave a history of low-back pain, and all but 3 presented abnormalities of posture. The postural abnormalities were best demonstrated by roentgenologic — particularly in the cervical region. Examinations

of the entire spine may be helpful in the evaluation of the postural and arthritic problem.

If the possibility of radiculitis is borne in mind, the diagnosis can be made in most cases on the basis of a carefully taken history and the physical examination. The importance of recognizing radiculitis and differentiating it from coronary-artery disease cannot be overemphasized.

## CASE REPORTS

**CASE 1.** F. W., a 64-year-old dentist, was first examined by one of us (D. D.) on January 15, 1945. He gave a history of two episodes of prolonged substernal pain. The first, which had occurred 5 years previously had been accompanied by weakness and had persisted for several hours. The second 8 weeks prior to examination, had been similar but less severe. These attacks were not followed by a rise in temperature and three electrocardiograms taken after the second attack showed no evidence of coronary artery disease.

Physical examination of the heart was negative, except for a slight systolic murmur over the midsternum. The blood pressure was 175/110. An electrocardiogram was within normal limits. Two months later the patient complained of pain in the region of the dorsal spine which was worse at night and radiated to both sides of the chest. It was relieved by keeping the spine erect and was aggravated by stooping. There was marked tenderness over the tenth dorsal vertebra and pressure in this region caused acute pain radiating anteriorly. The blood pressure was 160/90. X-ray studies of the cervical spine showed anterior and posterior marginal osteophytes, disk narrowing, osteoarthritic changes in the fifth and sixth intervertebral joints and scoliosis. In the dorsal spine there were large osteophytes along the anterior margins of the third to ninth vertebrae.

One week later the patient experienced an attack of severe substernal pain while sitting in a theater. It began in the dorsal region and radiated to the anterior portion of the chest, where it was felt as a squeezing pressure sensation. He recognized it as similar to the distress noted 5 years previously. It was severer than the earlier attacks and required morphine for relief. On examination the heart and lungs were normal. Moderate pressure over the sixth and seventh dorsal vertebrae precipitated severe pain, which radiated around the chest wall to the substernal region. The pain was elicited with difficulty when the patient stood erect or hyperextended the spine. The response to orthopedic treatment was prompt. On several occasions during the following year he experienced substernal constriction on stooping and occasional mild pain in the right shoulder region. On several examinations, tenderness was present in the region of the second to fifth left costochondral junctions. The posterior cervical muscles were spastic, and neck rotation was limited. On two occasions the patient had attacks of persistent vertigo aggravated by bending or moving the head from side to side and relieved promptly by traction therapy.

**CASE 2.** I. B., a 36-year-old man, was seen on April 20, 1946, complaining of attacks of severe substernal pain and pain in the left side of the chest of 5 weeks duration. The pain started in the interscapular region and radiated to the midportion of the sternum and precordium. On several occasions it awakened him at night and was present in the morning just after he got out of bed. Recently, the pain had recurred intermittently during the day and the nocturnal attacks had become more pronounced. Pain was brought on or aggravated by bending, prolonged sitting, deep inspiration, or coughing. A week previously the patient had had a severe attack after lifting a heavy weight. It had started as a "cramp" between the shoulder blades localized in the region of the anterior midportion of the chest, and had lasted for about 10 minutes. Two days later it recurred with greater severity while he was walking cannot stop. After some time he slowly made his way to the office. He was pale and in obvious distress. He tried to catch his breath and stated that his "wind" The respiratory disturbance and substernal pain recurred intermittently for several hours.



Examination of the heart and lungs revealed no abnormalities. The blood pressure was 130/90. There was marked spasm of the posterior cervical muscles, with limitation of head rotation and a moderate kyphosis of the upper dorsal spine. There was localized tenderness over the seventh and eighth dorsal vertebrae, and firm pressure caused substernal and precordial distress similar to that in the spontaneous attack. Simultaneously, the breathing became rapid and shallow. An electrocardiogram with six standard chest leads was within normal limits.

Roentgenologic examination showed slight osteophytic changes in the cervical and dorsal regions and pronounced postural changes. There were scoliosis and straightening in the cervical region and dorsal kyphosis. The response to orthopedic treatment was dramatic, with complete disappearance of symptoms, which have not recurred during the past 2 years.

### SUMMARY

The clinical and roentgenologic findings in 43 patients complaining of attacks of substernal or precordial pain of nerve-root origin (radiculitis) are analyzed. The location, character and radiation of the pain closely simulated coronary-artery disease.

The diagnosis of radiculitis was based on at least two of the following attacks of pain in bed, with change in bodily positions, and on coughing, sneezing or straining at stool, reproduction of the attacks by pressure over the dorsal spine and a striking response to orthopedic therapy.

In addition to the generally recognized features of dorsal-spine radiculitis, particular attention is called to the occurrence of a peculiar respiratory distress of radicular origin that may easily be mistaken for a manifestation of heart disease. The value of parasternal tenderness as a sign of dorsal-root irritation is also emphasized.

The patients, in addition to irritation of the dorsal nerve root, showed a high incidence of symptoms and signs of cervical radiculitis, such as shoulder-girdle pain, suboccipital headaches, vertigo, muscle spasm, tenderness and limitation of neck rotation.

Roentgenologic examination of the dorsal and cervical spine showed a high incidence of postural and osteoarthritic changes. The changes in the cervical spine may be summarized as follows: disk narrowings, 18 cases, anterior osteophytes, 39 cases, posterior osteophytes, 23 cases, osteoarthritis of the intervertebral joints, 11 cases, scoliosis, 31 cases, straightening, 23 cases, increased lordosis, 5 cases, kyphosis, 1 case, and osteoporosis, 22 cases.

In the dorsal spine, there was disk narrowing in 7, anterior osteophytes in 39, posterior osteophytes in 4 and scoliosis in 30 cases.

The roentgenologic findings demonstrate the location, nature and extent of the osteoarthritic changes in the spine and are of some value to the clinician when the symptoms are of short duration, the attacks cannot be reproduced or the radicular characteristics are not clear.

The recognition of radiculitis and its differentiation from coronary-artery disease are of practical importance in therapy and prognosis.

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## UTERINE CANCER ITS EARLY DETECTION BY SIMPLE SCREENING METHODS\*

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UNTIL the cause of and a specific cure for cancer have been found, successful treatment must depend on early diagnosis. Since symptoms suggestive of cancer may not appear until the disease is well advanced, early diagnosis must be made by a process of "screening" whereby symptom-free persons are examined at frequent intervals and studies made to detect malignant lesions.

The most frequent cancers in women are those of the uterus, both cervix and corpus, which comprise about 30 per cent of all malignant tumors in women, lesions of the cervix predominating over those of the corpus about 5:1. Early malignant lesions of the uterus are readily amenable to treatment, and five-year survival rates of 100 per cent may be expected if the cases are treated sufficiently early. Fortunately, the uterus, especially the cervix, offers opportunity for "screening" and the diagnosis of early lesions with very little inconvenience and expense to the patient.

A year ago we started a clinic for the early detection of cancer of the uterus at the Boston City Hospital. All the departments of the hospital have been requested to refer as many women over thirty-five years of age as possible to the Gynecological Clinic for "screening." This consists of a careful gynecologic history, with special attention to abnormal bleeding and vaginal discharges, a pelvic examination, a speculum examination and a vaginal smear. The last is most valuable as a test to determine cases that may require diagnostic curettage or cervical biopsy, not otherwise indicated by the history and pelvic examination. Cases that are positive on smear, or suspicious on smear, history or pelvic examination are subjected to biopsy by curettage or cervical biopsy, or both. If either of these procedures is positive the patient is referred to the Tumor Clinic for treatment. We never institute treatment on the evidence of a positive smear alone. If the case is suspicious but with a negative biopsy the patient is seen at least once a month in our special clinic, where more smears and possibly more biopsies are taken. In all obviously negative cases the patients are seen every six months for re-examination. In addition, one of the major interests in this study was to determine whether or not unsuspected cases of carcinoma could actually be detected by the vaginal smear.

## TECHNIC

The vaginal smear for the diagnosis of cancer of the uterus was introduced by Papanicolaou in 1928. Its value is based on the fact that carcinomatous lesions of the cervix and endometrium are exfoliative. The cancer cells are shed and collect in a pool in the posterior fornix together with cells from the endometrium, cervix and vaginal mucosa. Material for the smear is obtained by aspiration with a slightly bent, hollow glass tube of small caliber at one end of which is a rubber bulb. The glass tube must be absolutely dry. No douche or lubricant should be used prior to the taking of the smear. The tube with the rubber bulb compressed is inserted high into the posterior fornix and moved from side to side as the pressure on the bulb is released. The fluid thus obtained is blown onto a clean glass slide and smeared quickly, and the slide is immediately dropped into equal parts of 95 per cent alcohol and ether for fixation for at least thirty minutes. Care must be taken that the smear does not dry. Smears may be kept in the fixative for as long as two weeks before staining. The staining is done by the Papanicolaou technic, which is particularly adapted for delineating nuclear detail. For the most part only one smear was made in each case, but in many cases two or three were made.

## CYTOLOGY

The cellular characteristics of the vaginal smear, which have been extensively described by several authors,<sup>1-3</sup> are not dealt with in great detail. However, a brief description is in order for the purposes of this paper.

To recognize the abnormal cells in a smear it is essential to know the appearance of the normal cells. The most prominent of the normal cells are the large pavement-like cells that are desquamated from the superficial layers of the stratified squamous epithelium of the vagina and cervix. They are characterized by a small nucleus, an abundant cytoplasm and an irregular angular cytoplasmic edge. The cornified type of superficial cell has a pink cytoplasm and a pyknotic nucleus. The less common precornified type has a blue-green cytoplasm and a somewhat larger nucleus.

The basal-type cell which is derived from the deeper layers of the epithelium is a smaller round cell with green-staining cytoplasm and a relatively larger nucleus in proportion to the amount of cytoplasm. These cells are seen most frequently in postmenopausal patients but may be found in any smear.

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Very rarely does one find a smear that does not contain polymorphonuclear leukocytes, and these are readily recognized as small round cells with lobulated nuclei and a pale-green cytoplasm.

Red cells are often present in negative as well as in positive smears. Meigs et al.<sup>2</sup> state that red cells or red-cell debris is always found in positive smears and that the diagnosis of cancer is never made without some evidence of blood.

Histiocytes are found in negative and positive smears, more often in the latter. The nucleus is round or ovoid and contains finely stippled chromatin. The cytoplasm may be relatively scant but usually is abundant and filled with phagocytized debris such as red cells, fat vacuoles or polymorphonuclear leukocytes. They are sometimes difficult to distinguish from malignant cells since some malignant cells have phagocytic properties. The major feature in distinguishing these two cell types lies in the difference in the nuclei.

Benign giant cells are occasionally found, and these are large multinucleated cells with the nuclei located at the periphery of the cytoplasm. The nuclei have finely stippled chromatin and show little variation in size or shape.

Endometrial cells usually occur in small and large groups. They have round or ovoid regular nuclei with a finely granular nucleoplasm and a very scant amount of cytoplasm. They are found frequently during the later stages of menstruation, and in some cases these normal endometrial cells are seen in adenocarcinoma of the uterine body. Therefore, the presence of endometrial cells as well as red cells should arouse suspicion, and if no tumor cells are present on the smear, repeat smears should be done.

The diagnosis of cancer is almost entirely based upon nuclear changes. The cytoplasmic stain is extremely variable. Some tumor cells have green cytoplasm, whereas others have a bright-red cytoplasm.

These cells possess several features that stamp them as malignant cells. The nuclei are large in proportion to the amount of cytoplasm, in some cases no cytoplasm is visible. The nuclei may contain a large prominent nucleolus, or the chromatin may be distributed in coarse clumps. The nuclear edges may be wrinkled and folded, and the nucleus may appear as one solid, purple mass. When groups of cells occur together the extreme variation in the size and shape of the nuclei is readily demonstrated. Another point that aids in recognition of tumor cells is the fact that the cytoplasmic borders are indistinct and hazy. This is in contradistinction to most clusters of normal cells.

A few distinct types of cells are recognizable and are almost pathognomonic of cancer. The so-called "tadpole cell" is one of these. It has a rounded mass of cytoplasm which contains the nucleus, and a long cytoplasmic tail, which gives it the appearance of a tadpole. This cell is found in squamous-cell

carcinoma of the cervix. Another distinctive cell is the "spindle cell," which has the shape of a fibrocyte, with an elongated nucleus, and long thin spindles of cytoplasm on either side of the nucleus. This cell is a modified epithelial cell and is also seen in squamous-cell carcinoma of the cervix.

Tumor giant cells contain several large nuclei, which vary in size and shape and which are usually in the central portion of the cell. The nuclear differences distinguish them from the multinucleated giant cells of inflammatory origin.

Mitotic figures are rarely encountered. During the course of this study, none were seen. Papanicolaou and Traut<sup>4</sup> have had a similar experience and point out that, since the cells found in vaginal fluid are dead and desquamated, one would not expect to find mitotic figures in the smear.

The majority of smears from patients with carcinoma contained numerous malignant cells, many in groups, and were therefore not difficult to diagnose. On the other hand, a few were extremely difficult to diagnose because only one or two malignant cells were present. In 1 case a positive diagnosis was made upon the finding of one tadpole cell. Red cells and histiocytes were also present on the smear. In another case the diagnosis was made by the presence of one spindle cell. Both diagnoses were confirmed by biopsy and serve to illustrate the paucity of malignant cells in some positive smears.

## RESULTS

Many obvious cases of cancer were included in the study to demonstrate the various types of cancer cells and to provide definitely positive smears for comparison with questionable smears in which the exfoliated cells were few in number. In the 639 cases 934 slides were examined, and 357 biopsies were performed. The number of cases of carcinoma determined by biopsy was 54, including 43 cases of epidermoid carcinoma of the cervix, 2 of adenocarcinoma of the cervix and 9 of adenocarcinoma of the corpus uteri. The number of cases of carcinoma with positive smears was 51, and false-negative smears (negative smear, positive biopsy) were noted in 3 cases. The number of cases with negative smears was 585, with false-positive smears (positive smear and negative biopsy) in 12 cases. There were 42 cases of clinically obvious carcinoma, 6 cases of suspected carcinoma confirmed by biopsy and smear simultaneously and 6 cases of carcinoma unsuspected clinically, diagnosed primarily by vaginal smear and subsequently confirmed by biopsy.

Of 54 cases of carcinoma of the uterus a positive vaginal smear was obtained in 51—an accuracy of 95 per cent. Two of the patients from whom a false-negative smear was obtained had vesicovaginal fistulas, and there were very few cells on the slides. The other patient was bleeding, and the blood diluted the vaginal fluid to such an extent that erythrocytes and polymorphonuclear leukocytes were

the only cells seen. These three cases were all examples of far-advanced carcinoma. Fortunately, it is in the clinically obvious cases of carcinoma that the smears may be incorrectly regarded as negative and usually not in the cases of early carcinoma.

Of the 585 patients demonstrated not to have cancer a correct negative diagnosis was made in all except 12. These 12 cases constitute the false-positive group. This is 2 per cent of the cases diagnosed negative by smear and 4 per cent of the 303 cases proved negative by biopsy. This is a low percentage of error, but the fact that a false-positive diagnosis is made at all restrains one from undertaking therapy on the basis of the smear alone. No treatment has been instituted in this clinic without a positive biopsy.

One of the most interesting features of this study was the fact that 6 cases of carcinoma were diagnosed primarily by vaginal smear. An additional case of this type has recently been examined in this clinic and serves to illustrate the usefulness of the vaginal smear. The patient was a twenty-seven-year-old



FIGURE 1. Smear in Case 3 Showing a Group of Three Malignant Cells ( $\times 250$ )

woman who entered the clinic in January, 1947, when a smear and biopsy were taken. The smear was diagnosed positive and a tentative diagnosis of carcinoma in situ was suggested. However, the biopsy revealed a condyloma acuminatum. This smear was considered to fall in the false-positive group. The condyloma was treated, and the patient sent home. In October, 1947, the patient again entered the clinic, and another smear was taken but no biopsy was done. The smear was diagnosed positive, and showed many more tumor cells than the smear taken in January. The patient was brought back to the hospital and a biopsy done. The pathological diagnosis of the tissue was carcinoma in situ.

The following brief abstracts are typical of cases in this group. In Cases 3, 4, 5, 6, 7 and 12 the diagnosis was made primarily on the basis of the vaginal smear.

CASE 1. L. S. (B.C.H. 619 350), a 42-year-old woman, had had a supravaginal hysterectomy 14 years previously. There had been slight bleeding for 2 weeks. A small 1-cm erosion of the cervix was present. A vaginal smear was positive. A cervical biopsy showed epidermoid carcinoma.

CASE 2. M. M. (B.C.H. 785 292), a 58-year-old woman, had been treated for carcinoma of the cervix by radium and x-ray therapy in another hospital in 1940. No pain or bleeding had subsequently occurred. An irregular, pinched-out



FIGURE 2. Smear in a Case of Epidermoid Carcinoma of the Cervix Showing Tadpole Cells ( $\times 250$ )

area was seen on the left side of the cervix. A vaginal smear was positive. Biopsy showed epidermoid carcinoma.

CASE 3. M. K. (B.C.H. 546,329), a 71-year-old woman had no symptoms. A routine vaginal smear was positive (Fig. 1). Cervical biopsy showed epidermoid carcinoma.

CASE 4. B. C. (B.C.H. 555,284), a 76-year-old woman had had slight bleeding for 1 month. The cervix appeared normal. The uterus was small and regular in contour. A smear was positive. Uterine curettings showed adenocarcinoma.

CASE 5. A. B. (B.C.H. 699 977), a 43-year-old woman, had had a supravaginal hysterectomy for fibroids. At follow-up examination in the outpatient department a routine vaginal smear was taken. The smear was positive (Fig. 2). Biopsy of the cervix showed epidermoid carcinoma.

CASE 6. A. W. (B.C.H. 811 599), a 76-year-old woman, on August 3, 1946, had a diagnostic curettage and cervical biopsy because of bleeding. No carcinoma was found. On October 23 a vaginal smear was positive. Repeated curettings showed adenocarcinoma.

CASE 7. E. O. (B.C.H. 804 661), a 47-year-old woman had had a total hysterectomy for adenocarcinoma of the corpus uteri in October 1945. This had been followed by twenty x-ray treatments. There were no symptoms. A vaginal smear on August 7, 1946, was positive. Careful examination revealed a 0.5-cm. excavation at the right lateral angle of the scar in the vaginal vault. The first two biopsies from this area were negative for carcinoma, but the smears continued to show cancer cells. A third biopsy showed two small foci of carcinoma in lymphatic vessels.

CASE 8 R M (BCH 776,863), a 43-year-old woman, had menopausal menorrhagia. A smear was positive. Diagnostic curettage showed hyperplasia of the endometrium,



FIGURE 3 Section of Tissue in Case 10

Note the desquamated portion of the tumor lying in the gland-like space in this adenocarcinoma (x150)

with an area of squamous metaplasia to be regarded as potentially malignant

CASE 9 D G (BCH 1,222,039), a 50-year-old woman, had a positive routine smear. Biopsy of the cervix and curettings were reported as showing chronic cervicitis, the

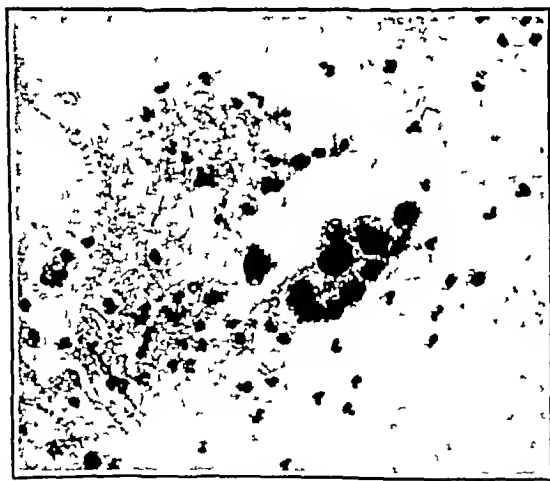


FIGURE 4 Smear in Case 10, Showing a Group of Malignant Cells (x250)

endometrium revealed inflammation with areas of markedly atypical squamous metaplasia of epithelium, which suggested early carcinoma

CASE 10 G D (BCH 1,214,073), a 51-year-old woman, had no symptoms. A routine smear was positive, and curettings showed well differentiated adenocarcinoma (Fig 3 and 4)

CASE 11 L J (BCH 849,782), a 29-year-old woman, complained of intermenstrual bleeding for 2 months. Two years previously she had been told that she had an erosion of the cervix but had received no treatment. The vaginal smear was positive. There was a 1-cm area of ulceration on the left lateral aspect of the external os. Biopsy showed epidermoid carcinoma of the cervix

CASE 12 M F (BCH 943,129), a 35-year-old woman, gave a typical history of endometriosis, and the diagnosis was confirmed by operation. There had been no abnormal vaginal bleeding. A routine smear prior to operation was positive. Speculum examination revealed a small, reddish area on the posterior vaginal wall at the junction of the portio with the vaginal mucosa. Biopsy from this area was reported as showing epidermoid carcinoma

## DISCUSSION

From our experience we believe that this method of screening is simple and efficient and definitely aids in the diagnosis of carcinoma. The degree of accuracy, of course, depends on the care with which the smears are taken and the training and experience of the cytologist. Although errors are made and the smear technic should never supplant meticulous biopsy, nevertheless, as Gates and Warren<sup>3</sup> aptly state in their excellent treatise on the subject, "The thing that matters primarily is whether the use of the method will discover cancer and initiate treatment earlier than would otherwise be done." In our series we have encountered 6 cases of carcinoma that we believe would have been treated at a much later date if the vaginal smear had not been used. In addition, 6 cases of carcinoma were diagnosed by the ordinary methods of examination as a result of the establishment of this clinic

## SUMMARY

A screening clinic for the detection of early carcinoma of the uterus is described, with especial emphasis on the vaginal smear

In one year 639 cases were examined, and 934 smears studied

Of 54 cases of cancer, 51 were diagnosed correctly by smear

Six cases of carcinoma, which might otherwise have been neglected, were detected by the vaginal-smear technic, and 6 others were detected simultaneously by biopsy and smear.

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## BRILL'S DISEASE\*

## Report of Two Serologically Proved Cases of Typhus Fever in Irish-Born Residents of Boston

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## BOSTON

THE name Brill's disease is usually given to the isolated cases of typhus fever that occur in the coastal towns of the northeastern United States.<sup>1</sup> In 1934 Zinsser<sup>2</sup> showed that these cases develop almost exclusively in immigrants from areas where there have been epidemics of louse-borne typhus fever. He demonstrated that the rickettsias that he was able to isolate from a few of these patients resembled the causative agent of epidemic or louse-borne typhus fever but that the disease was not associated with louse infestation. He came to the conclusion that Brill's disease represented a recrudescence of a latent infection of louse-borne typhus acquired while the patient had lived in an area where the disease occurred. Recently, Plotz<sup>3</sup> has presented serologic studies on several cases in Jewish immigrants that support this concept.

In Zinsser's<sup>2</sup> series of over 500 cases about 80 per cent were in Russian-Jewish immigrants, whereas only 4 cases were reported in persons from Ireland. The diagnoses in most of these cases were made on clinical grounds alone.

Two cases of Brill's disease in Irish-born Americans who have lived in Boston for many years are presented below, with serologic evidence that their illness was due to an infection with the causative agent of epidemic or louse-borne typhus fever. These two cases are of additional interest since the clinical findings were consistent with a diagnosis of primary atypical ("viral") pneumonia until the appearance of the rash.

## CASE REPORTS

**CASE 1.** C. C., a 56-year-old longshoreman had felt perfectly well until September 8, 1946, when he became weak and dizzy while unloading cargo from Chile. On the next day he had a shaking chill followed by a frontal headache. On September 10, when he was seen by a physician, the temperature was 104°F. He continued to have chills and chilly sensations and a marked feeling of malaise until he entered the hospital on September 14.

The patient had been born in Galway, Ireland and had come to Boston in 1910 at the age of 20. He had not left this area during the past 20 years. He denied any serious childhood illness to Ireland and could not remember any febrile illness in his family associated with a rash. He had been

treated in this hospital in 1914 for "blood poisoning" following an infection of his right hand.

Physical examination revealed a patient who appeared flushed and somewhat somnolent and who complained of severe headache. The skin was warm, dry and free of any eruption. The sclerae and conjunctivae were injected and slightly icteric. Examination of the chest revealed slight dullness to percussion over the right lower lung posteriorly and some slightly decreased breath sounds over this area. The findings in the heart and abdomen were within normal limits.

The temperature was 104°F by rectum, the pulse 98, and the respirations 26. The blood pressure was 134/60.

On the 20d hospital day, the patient developed a rash consisting of small, red maculopapular lesions on the chest and back with a few lesions on the upper arms. These faded gradually during the next 4 to 5 days. The temperature remained elevated to about 104°F until September 19. During that time the patient continued to be somewhat somnolent and lethargic and exhibited twitching of the arms and hands and facial grimaces. Treatment consisted of about 4500 cc. of fluids daily during the febrile period and, beginning on September 17, 30,000 units of penicillin intramuscularly every 3 hours for 11 days. On September 19 the temperature began to fall, reaching normal levels on September 23. During that time the patient showed marked subjective improvement. He was discharged on October 3.

On admission the urine had a specific gravity of 1.008 and gave a + test for albumin and a positive test for bile. The blood hemoglobin was 94 per cent, and the white-cell count 6650 with 81 per cent neutrophils, 14 per cent lymphocytes and 5 per cent monocytes. The white-cell count was 10,000 on September 16 and then returned to normal. The initial icteric index was 25, and this decreased to 10 by September 18. The blood ooprotein nitrogen was 42 mg per 100 cc. and fell to 25 mg by September 18. The serum cephalin flocculation was ++, the prothrombin time was 85 per cent of normal and the formal-gel test was negative. Lumbar puncture showed a clear spinal fluid with 3 or 4 lymphocytes and 3 erythrocytes per cubic millimeter and a total protein of 11 mg per 100 cc. Several blood cultures showed no growth. Cultures of the first specimen of urine yielded *Pseudomonas aeruginosa* and *Escherichia coli*, but subsequent ones were negative. An electrocardiogram on September 20 showed a normal sinus rhythm with a partial auriculoventricular block, the PR interval being 0.23 second, another tracing 6 days later disclosed a PR interval of 0.20 second. X-ray films of the chest taken at the time of entry and again 3 days later revealed areas of diffuse, finely mottled density in both lower lungs and in the right middle-lung field consistent with primary atypical pneumonia. Another film taken 8 days later showed clear lung fields.

Agglutination tests with organisms of the typhoid Salmonella group *Brucella abortus* and *Pasteurella tularensis* were negative. Cold hemagglutination and heterophil antibody tests were also negative. Complement fixation tests with the antigen of Rocky Mountain spotted fever and agglutination tests with *Proteus vulgaris* strains OX2 and OXK were negative. The results of the Weil-Felix test (agglutination of *P. vulgaris* strain OX19) and of tests for antibodies against the rickettsias of epidemic and murine typhus are shown in Figure 1.

**CASE 2.** S. E., a 51-year-old laborer, entered the hospital on October 2, 1947. He had been entirely well until September 29 when he had caught cold. That evening he felt weak and nauseated and went to bed without eating. During the night he had repeated shaking chills followed by drenching sweats. Later he developed a dry, hacking cough which occurred hourly in paroxysms lasting 5 to 10 minutes. On

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the appearance of the rash, the character and distribution of which suggested the possibility of a rickettsial disease. Since the rash in Brill's disease is frequently absent or consists only of a few macules, the diagnosis might easily have been missed.

The diagnosis of a rickettsial infection was made by serologic methods. The rising titer of agglutinins for *P. vulgaris* (strain OX19) was consistent with a diagnosis of typhus fever. Endemic or murine typhus could not be ruled out in these cases on clinical or epidemiologic grounds. Epidemic or louse-borne typhus does not occur in this area since living conditions in general do not provide a louse-infested population, which is necessary for its spread and maintenance. Furthermore, if louse infestation were a factor, other cases from the same home might be expected. Since both patients had been born in Ireland, where epidemic typhus has occurred, they were thought probably to have Brill's disease.

In both cases, the fact that the patients spent considerable time on the docks raised the question of possible infection from a shipboard source. This was particularly true of the patient in Case 1, who had been unloading cargo from Chile at about the time he became ill. Murine typhus was considered as a possible diagnosis, but the incubation period would then have been very short if the disease had been acquired from rats on this ship. However, on close questioning both patients were discovered to have come to the United States from County Galway, Ireland, where louse-borne typhus is known to occur. This area was the site of a serious epidemic in 1903-1905,<sup>4</sup> and an outbreak of over 134 cases occurred there as recently as 1942. The typhus epidemic of 1903 occurred when the patients were thirteen and seven years of age, respectively. Since typhus fever is often a mild disease in childhood, both patients could have been infected during this outbreak without an illness of such severity as to be readily remembered.

In both patients, the clinical course of the disease was consistent with that seen in Brill's disease. The low initial white-cell counts, which rose to 10,000 or more during the second week, are frequently observed in such cases. The development of thrombophlebitis as a complication in Case 2 was of particular interest since patients with typhus fever often develop thromboses of blood vessels.

The suspicion that these patients were having a recrudescence of a previous attack of louse-borne typhus fever was confirmed by the rickettsial serologic studies noted in Figures 1 and 2. The rickettsial complement-fixation tests gave consistently higher titers with the epidemic antigen as compared with those obtained with the murine antigen. This difference is considered to be diagnostic of epidemic typhus fever.\* In most cases, the rickettsial agglutination tests showed similar differences in

titers. The difference in titers was still demonstrable in Case 1 a month and again eleven months after the illness, and in Case 2 the difference was observed two months after the acute disease. Neither of these patients had received any typhus vaccines. The findings seem to rule out the possibility that the high titer to the epidemic antigen was due to the fact that these patients had had epidemic typhus fever as children with a marked rise in antibody titer for this antigen as an anamnestic reaction during an attack of murine typhus. If that had occurred, one would have expected the epidemic titer to fall off more rapidly. In these patients, the rickettsial agglutination tests seemed to show less specificity with most serum specimens than the complement-fixation tests.

The Weil-Felix agglutination tests in both patients are consistent with a diagnosis of typhus fever in that the titers with *P. vulgaris*, strain OX19, show a rise in titer, whereas there are no significant titers with strain OX2 or OXK. It is of interest that in Case 1, in which a titer of agglutinins of 1:2560 for strain OX19 developed during the course of the illness, these agglutinins were easily detectable almost a year later, whereas the titer in Case 2 fell rapidly during convalescence. The negative results in the complement-fixation tests for Rocky Mountain spotted fever in Case 1 and for Q fever, rickettsialpox and psittacosis in Case 2 eliminate them as possible diagnoses.

It appears most likely, therefore, that the illness in these cases was Brill's disease—the recrudescence form of epidemic typhus fever—occurring as a sequel to an attack of typhus fever during childhood in Galway, Ireland.

The diagnosis of Brill's disease should be considered in any foreign-born American regardless of race, who comes from an area where epidemic typhus occurs and who suffers from an acute febrile illness characterized by severe headache, chills and fever with or without a skin rash.

#### SUMMARY

Two cases of Brill's disease occurring in Irish-born persons who had lived in Boston for many years are described. The clinical features were consistent with the diagnosis of primary atypical (viral) pneumonia until the appearance of the rash, which was characteristic of that seen in rickettsial infections. The diagnosis of the recrudescence form of epidemic or louse-borne typhus fever was established by serologic methods.

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\*Both Drs. Cox and Sussel, in personal communications, expressed the opinion that these results were diagnostic of epidemic typhus.



## THE USE OF BENADRYL IN PARKINSON'S DISEASE

## A Preliminary Report of 8 Cases

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**P**ARALYSIS agitans, or Parkinson's disease, is a chronic progressive disease of the corpus striatum and extrapyramidal motor system for which there is no known cure. Treatment has always been symptomatic, and useful drugs have been limited almost entirely to those in the atropine series. These have consisted of hyoscine, hyoscyamine, belladonna and stramonium, either individually or in various combinations. Amphetamine (benzedrine) sulfate has occasionally been beneficial in relieving some of the symptoms, but its mechanism of action has never been clearly explained.

The use of benadryl in paralysis agitans was first tried on a patient in September, 1946, on a purely empirical basis. The result was so gratifying that other subjects with paralysis agitans were also given the drug to determine whether the improvement noted in the first patient was simply an unusual response in a suggestive person or whether the reaction could be consistently reproduced in others. There is no literature on the use of benadryl in paralysis agitans, but McGavack, Elias and Boyd<sup>1</sup> mentioned its use in 4 patients, with improvement in 3.

## CASE REPORTS

**CASE 1** J C, a 57-year-old man, had been suffering from Parkinson's disease for 14 years. He had a typical mask-like face and a pill-rolling tremor of the fingers. The voice was high pitched and thin. He stood with the knees bent and the back stooped forward. He could walk only a few steps before starting to run to maintain balance. Even then he could go only about 10 yards before he clutched at any object in his path to keep from falling. There was no past history of encephalitis.

The patient was in the hospital for 5 months and obtained the usual slight benefit derived from stramonium and scopolamine. On September 24, 1946, the scopolamine was discontinued and 50 mg of benadryl four times daily was begun. In a few days marked improvement was noted. The patient volunteered the statements that he was walking better, swallowing was easier, he was less nervous and shaky, the legs felt stronger and drooling from the mouth had stopped. Several independent observers in the ward noted that he could walk a much greater distance before he started running, and that he could stop himself at any time without the need of supporting himself on some object in his path.

On October 4 the amount of benadryl was doubled, and the stramonium was discontinued so that the patient received nothing but benadryl. With the increase of benadryl dosage, a pounding and humming in the ears, but no further improvement in symptoms, was noticed. The tremor, in fact, seemed somewhat aggravated. The amount of benadryl was then reduced to the original daily dose of 200 mg and scopolamine three times daily was added to this therapy. It was noted that the patient had less tremor and felt less nervous when the scopolamine was given in addition to benadryl.

On May 9, 1947, an attempt was made to substitute pyribenzamine for benadryl, but after 4 days the patient begged for resumption of the benadryl. He remarked at that

time that he was sweating profusely and constantly and that locomotion was becoming poor. Upon a return to benadryl relief was noted within 3 days. This patient had been on 50 mg of benadryl four times daily and 0.6 mg of scopolamine three times daily for over 1 year when he was last seen. The initial improvement, noted shortly after the institution of benadryl therapy, had been maintained. There was no evidence that tolerance to the drug was developing. On the other hand, there was no evidence that the drug was producing any gradual or steady improvement in symptoms. Evidently, the original response, which had developed within the first few weeks, was not further improved by continued use of the drug or by raising of its dosage.

**CASE 2** H S, a 68-year-old man, had had typical Parkinson's disease for 4 years. The coarse tremor and hypertonicity of muscles were incapacitating. He was unable to dress or feed himself, and he had to be helped out of a chair when he tried to stand up. He walked with a typical shuffling gait, and the body was stiffly bent forward from the hips and shoulders. He was frequently awakened during the night by cramps in the muscles, which his wife had massaged for relief. Medication had consisted of eight "rabellon" tablets daily. There was no past history of encephalitis.

The patient was started on 50 mg of benadryl four times daily. Within 7 days he was able to stand up from a sitting position unaided. He was also able to dress himself and to handle a knife and fork, although with difficulty. It was noted that he often sat for 1 hour without tremor, and he was able to walk with longer steps and without shuffling. Within 2 weeks he was able to sit quietly in church for the first time in 3 years, and he even found it possible to sit quietly through a 3-hour symphony concert. The nocturnal muscle cramps disappeared, and he was able to sleep through the night without interruption. He gradually reduced the "rabellon" dosage to three tablets daily and he later remarked that he often did not take any for a day at a time. When this patient was last observed 3 months after starting benadryl therapy, he was leading a normal business and social existence without any apparent handicap from the occasional coarse tremor that at times became manifest.

**CASE 3** M F, a 66-year-old housewife, had been suffering from Parkinson's disease for over 5 years. The symptoms started mildly but gradually progressed. After 4 years she became nearly helpless and was hospitalized for 6 months. The only medication consisted of 0.15 gm of stramonium three times daily. She had complained of a "neuritis" in the right arm for 5 years, and during that period she had kept the arm close to the side of the body, using only the portion distal to the elbow joint. She complained of cramps in the knees, which kept her awake at night. There was no past history of encephalitis.

This woman demonstrated typical Parkinsonian tremor of fingers, chin and mouth. The face was mask-like. The walk was stiff, and the feet shuffled. The right arm was painful and was held stiffly against the side of the chest. Any attempt by the examiner to abduct the right arm or to extend the elbow was vigorously opposed by the hypertonic and rigid muscles. Forced motion of this arm caused severe pain. The patient was started on 50 mg of benadryl four times daily but was advised not to discontinue the stramonium. After 3 days of medication she gleefully greeted the physician, when he entered her room, by extending the right arm to shake hands. She remarked that she had been unable to do this for over 2 years. During the next 3 weeks she began to eat with a fork instead of using the fingers, to drink water from a glass instead of using a drinking tube, to fold a napkin, to make her own bed, to cut with scissors and to write a letter fairly rapidly and legibly. One of the first symptoms to disappear was a profuse and uncomfortable perspiration. The pain in the right arm disappeared entirely. An attempt was made to withdraw the stramonium, but the

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tremor seemed to increase without it. As noted in other cases, complete withdrawal of the parasympathetic inhibitory drugs caused some aggravation of symptoms.

**CASE 4.** S. B. A. 68-year-old man, had suffered from Parkinson's disease for 10 years. He had tried many types of therapy including pyridoxine administered orally and by injection. He had been taking four "rabbellon" tablets daily for 3 years before starting on 50 mg of benadryl four times daily. The patient had been unable to feed himself for the preceding 3 years and he had been unable to dress himself for the previous 8 months. He had the usual difficulty in walking and the feet scuffed the floor. He complained of a very annoying sialorrhea and dysphagia. He noticed improvement within 1 week after starting the benadryl therapy. The improvement continued and when he was last seen about 2 months after institution of therapy, the transformation was remarkable. He stated that he could dress and feed himself write his name legibly and even lie down or get up out of bed without help. Formerly he could not even sit down or stand up from a chair without assistance. He remarked that he could walk much farther without fatigue, and that the feet no longer scuffed the floor or the sidewalk. The sialorrhea and dysphagia disappeared. He noticed that he was less uncomfortable in hot weather after taking benadryl. He stated that at night he had formerly slept about 1 hour at a time before being awakened by a cramp in an extremity or by inability to turn in bed to a more comfortable position. He had obtained relief with sodium amylal, which he took frequently at bedtime. He found that benadryl enabled him to sleep all night, and he was able to dispense with the use of sedatives entirely. However, he was never advised to discontinue the rabbellon since, in the other cases it had been found that the parasympathetic-inhibitory drugs and the benadryl seemed to have a definite synergistic action.

**CASE 5.\*** A. B. A 65-year-old single woman, developed weakness and easy fatigability about 3 years before she was first examined. It was gradually noticed that tremor of the hands and fingers particularly on the left side, had developed. The weight dropped from 124 to 98 pounds and thyrotoxicosis was suspected. The basal metabolic rate was +37 per cent, falling to +24 per cent after 2 months of thiouracil therapy but without any clinical improvement. The patient was noted to have a mask-like face, coarse tremor of the hands and fingers and shuffling gait, and the trunk and spine were bent stiffly forward. On scopolamine therapy (0.4 mg twice daily) she showed considerable improvement even to the extent that the basal metabolic rate fell to +14 per cent. She was maintained on this therapy for 4 months and was then shifted to 50 mg of benadryl three times daily. She immediately noticed further improvement. There was much less fatigue, and she slept better and worried less. She found herself able to move about with a great deal more ease, but she had a temporary setback when she fell downstairs the accident probably being the result of overconfidence in her abilities. She showed no added improvement when the benadryl dosage was raised to 300 mg daily. The final dosage was maintained at 200 mg daily divided into four doses.

**CASE 6.** A. G. F. A 66-year-old housewife, had been suffering from typical Parkinson's disease for 2 years with slight relief from atropine. She was started on 50 mg of benadryl four times daily. When she was seen 1 month later there was a great deal of improvement in the tremor, and walking was better. She remarked proudly that she was able to write letters quickly and quite easily, whereas formerly a single letter took days to complete. She was later tried for several days on pyribenzamine in equal dosage, but there was an immediate aggravation of symptoms, which were at once relieved when she returned to Benadryl.

**CASE 7.** S. G. A 68-year-old woman was seen after a 2 year history of progressively increasing symptoms of Parkinson's disease. She was given 100 mg of benadryl three times daily with considerable improvement during the first few weeks but without much noticeable benefit thereafter.

**CASE 8.** O. N. A. A 72-year-old man was never seen by me or by my associates. He was suffering from Parkinson's disease and was advised by the patient in Case 2 to take

benadryl for his symptoms. The patient's wife stated that she and her husband were satisfied with the results. "If benadryl doesn't do any more than to continue to make our nights more restful, it will be wonderful we need to be up and down all night long just in a nervous dither but now after using it just 28 days he sleeps through the night. The neighbors remarked a noticeable change in the way the patient walked and turned around much more easily. He could also get up and out of chairs more easily."

The patient who had had this condition for about 11 years had previously received atropium which he had not taken since starting benadryl therapy.

## DISCUSSION

The obvious benefits derived from the use of benadryl in the cases reported above can hardly be considered due to the enthusiasm with which a new drug is often administered. The victims of Parkinson's disease are not readily subject to suggestion since they have all suffered from their illness too long to welcome a new therapy with much faith. However, the good results obtained in this small group may not withstand the test of larger series of cases.

The beneficial results are not readily explained. An atropine-like action of the drug has been described,<sup>2</sup> and its effect in Parkinson's disease may be similar to that of atropine. Furthermore, con- gestion of the choroid plexus has been observed in animals intoxicated with benadryl.<sup>1</sup> This effect may produce an enhancement of the circulation of the corpus striatum, where the symptoms of paralytic agitans are initiated.

## SUMMARY

Eight patients suffering from paralysis agitans, (Parkinson's disease), all of them in the arterio-sclerotic group, were treated with benadryl over a period varying from three to fourteen months. All patients noted considerable improvement in the symptoms so long as the drug was administered.

Four of the treated patients continued to use parasympathetic-inhibitory drugs of the atropine series, and there seemed to be a synergistic action between these drugs and benadryl. A closely related antihistamine drug, pyribenzamine, apparently was ineffective in the treatment of Parkinson's disease.

The possible mechanism of action of benadryl in this disease is briefly discussed. Its use is suggested as an added therapeutic weapon to be administered alone or in conjunction with the atropine-like drugs.

Since this paper was submitted for publication 2 additional cases of Parkinson's disease have been treated with benadryl. The response to the drug was excellent in both cases.

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\*I am indebted to Dr. Frank K. Padgett of Pittsfield, Massachusetts for permission to include Cases 5, 6 and 7.

## MEDICAL PROGRESS

### INTERCAPILLARY GLOMERULOSCLEROSIS

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CHARLOTTE, NORTH CAROLINA, AND RICHMOND, VIRGINIA

IN 1936 a small series of cases was reported by Kimmelstiel and Wilson<sup>1</sup> showing a conspicuous correlation between a syndrome of diabetes, nephrotic edema, gross albuminuria and hypertension and a peculiar type of intercapillary sclerosis of glomeruli. The nature of this investigation, taking its origin from systematic analysis of a large volume of autopsy material, precluded a specific detailed study of clinical features. The relatively scant clinical information was merely sufficient to emphasize the significance of the histologic findings. A large number of similar cases have been reported during the last twelve years, and with them a wealth of clinical experience has supplemented the sketchy notes that accompanied the original description.

Although, by and large, most authors confirmed these observations, an analysis of the literature has brought to light conflicting reports and divergent interpretations. The term "intercapillary glomerulosclerosis" has been maintained in most publications, a consoling circumstance for those who review the literature, but the name hardly veils the violent disagreement concerning the true nature of the condition. Many problems have been raised that still await clarification. The specificity of the glomerular lesion, the incidence of its occurrence, its relation to diabetes, the accurate definition of the clinical syndrome, the histogenesis and many other questions are still under discussion.

A survey of the literature has convinced us that many of the discrepancies originate from differences in the interpretation of histologic findings. It appears to us that this explains why some authors believe the lesion to be highly specific, whereas others use it to illustrate the general concept of nonspecificity of glomerular lesions.<sup>2</sup> It is also the obvious reason for wide variation in incidence reported by various authors, ranging from 15.0 to 63.7 per cent in autopsy material on diabetic patients. An attempt to clarify the histologic criteria must therefore precede consideration of the remaining problems.

#### SPECIFICITY OF GLOMERULAR LESIONS

All observers have readily recognized the striking and characteristic change of the glomeruli. If fully developed, it consists of a hyaline mass in the central portion of the glomerular lobules, creating the impression of being situated between the capillaries. Different authors, however, vary considerably in

their opinion concerning the specificity of this lesion for diabetes. Occurrence of intercapillary glomerulosclerosis in nondiabetic, arteriosclerotic kidneys has been reported as varying from 0.8 to 12.0 per cent,<sup>3,4</sup> and as high as 25.4 per cent (Horn and Smetana<sup>5</sup>). Siegal and Allen,<sup>6</sup> on the other hand, found typical changes in only 1 out of 100 nondiabetic, hypertensive patients, and Bell<sup>7</sup> states that he considers intercapillary glomerulosclerosis (of the nodular type) almost pathognomonic for diabetes. The relatively frequent occurrence of intercapillary glomerulosclerosis in cases of glomerulonephritis is discussed separately below.

All authors who observed intercapillary glomerulosclerosis in a significant number of cases in the absence of diabetes emphasize that the involvement was of "minimal severity" or of a mild degree. It seems, therefore, that previous statistics should be re-evaluated in the light of the criteria used for the recognition of the lesion.

No claim of specificity was made in the original report,<sup>1</sup> and the change in the glomeruli was described as representing merely an extreme degree of a process, milder forms of which are frequently found in nondiabetic kidneys of aged persons. Allen,<sup>8</sup> however, concluded from his detailed studies that the lesion under consideration is highly specific and differs not only quantitatively but also qualitatively from similar degenerative glomerular changes. His concept has been accepted in part by many writers. He showed that the hyaline mass contains markedly argentophilic laminated fibrils differing conspicuously in intensity of impregnation and arrangement from those seen in hyalin associated with nondiabetic glomerulosclerosis. Also noted was a relatively increased resistance to tryptic digestion of the "diabetic" hyalin in contrast to the nondiabetic hyalin. It is apparent that these criteria reinforce the contrast between diabetic and nondiabetic hyalinization, but in our opinion they do not establish a clear-cut line of cleavage between specific and nonspecific changes.

Bell<sup>7</sup> has attempted to clarify the situation by subdividing the glomerular changes into the nodular and the diffuse type.

#### Nodular Type

This change, consisting in sharply defined spherical bodies, is apparently the same as that originally designated as "severe degree."<sup>1</sup> The renal involvement can be graded according to the number of

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nodules per glomerulus and the number of glomeruli presenting the lesion

There can be no doubt that the nodular type is occasionally observed in cases in which diabetes can reasonably safely be excluded. Siegal and Allen<sup>8</sup> have presented convincing evidence in a patient who demonstrated all other components of the syndrome but whose fasting blood sugar level was within normal limits. Unfortunately, a glucose-tolerance curve was not determined. The overwhelming majority of such cases, however, are found in kidneys of diabetic patients. This lesion, according to Fahr,<sup>9</sup> "is seen infinitesimally more rarely in nephrosclerosis without diabetes," and Bell<sup>7</sup> considers this type almost pathognomonic for diabetes. With few exceptions most writers have concluded that the nodular (severe) type constitutes a reliable aid to the diagnosis of diabetes at autopsy. Even the authors who reported a relatively high percentage of intercapillary glomerulosclerosis in cases without diabetes observed that diabetes is rarely absent if the glomerular lesions are severe.<sup>1, 3-6, 10-12</sup> Dr. A. C. Allen, in a personal communication, goes so far as to say

In view of our experiences and those of our associates over the past years I am altogether convinced of the specificity of the nodular lesion which is the only lesion that is of current pertinence. I should strongly suspect that the finding of a nodular lesion in a non-diabetic means either that the mild form of diabetes mellitus, which these patients often have, has been overlooked, or that there has been a confusion of the definitive histologic criteria that this lesion possesses.

### Diffuse Type

Bell<sup>7</sup> does not give a detailed description of this lesion except for stating that it resembles the changes in chronic glomerulonephritis and is formed by splitting of the inner basement membrane. This type, according to Bell, may be present alone or in conjunction with the nodular type. Although it is not certain, it is most likely that the diffuse form is identical with what other authors have designated as "less severe degrees." This form is apparently more frequent in cases of diabetes than the nodular type, but at the same time is more common in non-diabetic patients.<sup>3, 4</sup> According to Bell<sup>7</sup> the nodular lesion occurred in 15.9 per cent of cases of diabetes, and the combined nodular and diffuse form in 29.2 per cent — that is, almost twice as often. It is inferred from Bell's description that the diffuse lesion is not always readily identified and correctly interpreted. Hence, no accurate estimate can be made of its specificity. The diffuse or less severe type of intercapillary glomerulosclerosis does not possess sufficient histologic characteristics to be distinguished from other intercapillary glomerular changes, and its relation to diabetes is yet to be explored. It is conceived by most authors as a forerunner of the nodular type. In its mildest form<sup>13, 14</sup> Wilson<sup>1</sup> linked it to a rather frequent glu-

change in senile kidneys, which they believed to be only indirectly connected with vascular sclerosis and which they were not able to correlate with diabetes. They termed this process "axial" glomerular thickening — an "aging" process. It is of interest to compare this interpretation of histologic findings with Goodof's<sup>2</sup> statement that the glucose-tolerance curve in older patients often approaches that of diabetes, apparently parallel to the aging process of the glomeruli.

The final proof of the specificity of intercapillary glomerulosclerosis, namely, the experimental reproduction of the lesion has been attempted by Lukens and Dohan.<sup>15</sup> These authors rendered a dog diabetic

TABLE 1 Frequency of Intercapillary Glomerulosclerosis Reported in the Literature

AUTHOR	INCIDENCE	APPROXIMATE RATIO OF MALES TO FEMALES
Allen <sup>8</sup>	33.0	—
Bell <sup>7</sup>	14.5	2.1
Goodof <sup>2</sup>	9.5*	10.7
Warner <sup>4</sup>	<20.0	—
Gracius	16.0	—
Herderman <sup>1</sup>	9.9*	2.1
Hernandez Morales and Diaz Rivera <sup>6</sup>	—	2.1
Average	17.1%	1:1

\*Corrected figures only such cases as are designated as advanced are used in this table.

with extract of the anterior lobe of the pituitary gland. The dog maintained diabetes during a five-year period. A post mortem examination revealed lesions in the kidneys resembling early lesions of intercapillary glomerulosclerosis.

In summary, an evaluation of available statistical data reveals that the nodular or severe type of intercapillary glomerulosclerosis can be regarded as almost specific for diabetes. If, however, the diffuse, or less severe type, is included in the statistics, the incidence of its occurrence in diabetes rises as its specificity falls. A clear distinction between the two types is therefore imperative if the concept of a specific "diabetic" glomerulosclerosis is to be saved.

### FREQUENCY

The survey of the literature does not permit final conclusions concerning the frequency of intercapillary glomerulosclerosis since it is not always possible to determine how strictly the histologic criteria have been applied. Even if confined to reports in which one can be reasonably certain that the nodular type is referred to, the figures vary greatly (Table 1). From a selection of such statistics, which lend themselves to reasonably secure interpretations, the conclusion is drawn that intercapillary glomerulosclerosis occurs in approximately 17 per cent of all cases of diabetes, about twice as often in women as in men.

It apparently occurs —

decades of life (Fig 1), only 3 cases being reported at the ages of sixteen,<sup>4</sup> seventeen,<sup>3</sup> and nineteen,<sup>3</sup> although the lesions were only of a mild or diffuse type in at least 1 of these cases (the degree was not

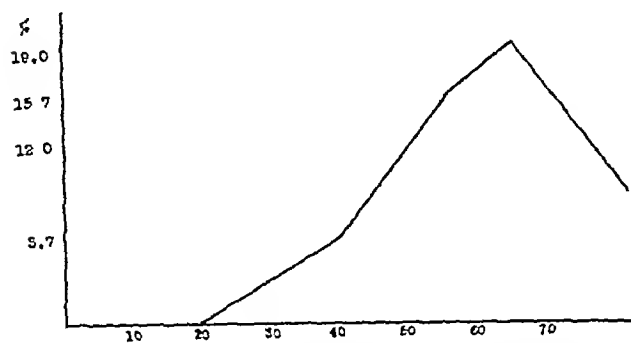


FIGURE 1 Occurrence of Intercapillary Glomerulosclerosis according to Decade of Life

clearly indicated in either of the other cases) After that a slow rise occurs in the third decade of life, although, again, these cases seem to be of milder degree.<sup>3</sup> The incidence subsequently rises further, to

in chronic glomerulonephritis.<sup>4, 16</sup> How often this occurs is difficult to estimate since most authors do not indicate the degree or type observed. In most cases it is relatively simple to segregate the diffuse type of intercapillary glomerulosclerosis in chronic glomerulonephritis from that in diabetes. The main distinguishing features have already been discussed by Kimmelstiel and Wilson<sup>1</sup> and later by others. Since intercapillary glomerulosclerosis begins in the center of the lobule and glomerulonephritis in the peripheral capillaries, the former usually shows widened peripheral capillaries with a clearly demarcated basement membrane, and the latter shows narrowed capillary lumens with a blurred basement membrane. Additional general criteria, as a rule, make the differentiation relatively simple.

Cases of chronic glomerulonephritis, however, are seen in which the kidneys show occasional, or even numerous, glomeruli indistinguishable from the nodular type of intercapillary glomerulosclerosis, and in these cases diabetes is known to be absent. Are the morphologic changes in these cases fundamentally the same or do they represent a different pathologic process? To our knowledge only one attempt has been made to answer this specific question. Henderson et al.<sup>16</sup> made a comparative clinical

TABLE 2 Points of Difference between Patients with Chronic Glomerulonephritis Associated with Intercapillary Glomerulosclerosis and Patients with Diabetes and Intercapillary Glomerulosclerosis

CONDITION	AVERAGE AGE OF PATIENTS	EDEMA	ALBUMINURIA	SPECIFIC GRAVITY	UREA NITROGEN	ANEMIA	RETINOPATHY	DURATION OF TERMINAL ILLNESS	CAUSE OF DEATH
Diabetes with intercapillary glomerulosclerosis	58	Less prominent	Less intense	Higher	Lower	Less severe	Diabetic type	Months to years	Varied
Glomerulonephritis with intercapillary glomerulosclerosis	32	More prominent	More intense	Lower	Higher	More severe	Hypertensive type	1 to 4 months	Usually cardiac, renal or infections

reach its maximum during the sixth decade, thereafter declining slightly. Bell's statistics seem to represent best the general impression gained from a survey of the literature.

In summary, intercapillary glomerulosclerosis of the nodular type occurs in approximately 17 per cent of all cases of diabetes, most frequently during the sixth decade of life.

#### RELATION TO CHRONIC GLOMERULONEPHRITIS

Clinically, these conditions may closely resemble each other. Diabetic patients with albuminuria, nephrotic edema, hypertension and renal insufficiency have often been diagnosed as having diabetes complicated by independent glomerulonephritis.<sup>6, 16</sup> Derow et al.<sup>19</sup> pointed out that aside from the age, the absence of previous history of acute glomerulonephritis may be the only information of differential significance.

There is no doubt that intercapillary glomerulosclerosis may occur in a significant number of cases

study that revealed the following facts: cases of chronic glomerulonephritis with or without intercapillary glomerulosclerosis show no significant clinical differences, and patients with chronic glomerulonephritis with intercapillary glomerulosclerosis differ from diabetic patients with intercapillary glomerulosclerosis in spite of superficial resemblances. Both groups have in common hypertension of varying degrees, albuminuria, edema and retinopathy. The points of difference are summarized in Table 2. This analysis clearly depicts the essential clinical differences between glomerulosclerosis and chronic glomerulonephritis in general. The authors conclude from this comparison that intercapillary glomerulosclerosis in diabetes constitutes a pathologic process different from intercapillary glomerulosclerosis accompanying chronic glomerulonephritis, although they closely resemble each other histologically. It should be taken into consideration, however, that most of the clinical differences are quantitative ones. It appears questionable that the pro-

found changes in protein metabolism and in renal function that occur in chronic glomerulonephritis could be altered perceptibly by the accompanying intercapillary glomerulosclerosis, which, by itself is associated with similar changes of a lesser degree. If intercapillary glomerulosclerosis of the diabetic type occurs in chronic glomerulonephritis, it may be expected that the related clinical symptomatology is completely masked by that of the glomerulonephritis. Only the retinopathy is different in quality in the two conditions, and, as pointed out below, this type of retinopathy is directly dependent upon the diabetes rather than upon the renal lesion.

We are therefore inclined to assume that the same process of intercapillary glomerulosclerosis that occurs in diabetes also occurs in chronic glomerulonephritis. The fact that it is relatively more common in glomerulonephritis than in any other disease except diabetes should prompt one to search for a metabolic disturbance prevalent in both conditions as the precipitating factor.

In summary, the clinical symptomatology of intercapillary glomerulosclerosis in diabetes and of chronic glomerulonephritis may resemble each other closely. Signs of importance in the differential diagnosis are briefly tabulated. Histologically, the lesion may be indistinguishable at times, although in the majority of cases, the differences are obvious. There is no reason to assume a difference in pathogenesis between diabetic intercapillary glomerulosclerosis and intercapillary glomerulosclerosis in chronic glomerulonephritis.

#### RELATION TO NEPHROTIC SYNDROME

If the nephrotic syndrome is defined as a condition characterized by albuminuria, hypoproteinemia, hypercholesterolemia and edema, it may be stated that this has not been reported in cases of diabetes without intercapillary glomerulosclerosis.<sup>4</sup> On the other hand, fully developed nephrosis does not often participate in the complex syndrome connected with intercapillary glomerulosclerosis. Albuminuria is present in most cases and seems to be roughly parallel to the severity of glomerular involvement,<sup>8</sup> but lesser degrees of albuminuria may be related to cardiac or other renal lesions. Exact figures in that respect are not available, but most authors agree that significant albuminuria (a +++ test) occurs in the majority of cases. However, Bell<sup>17</sup> reports that no albumin or a faint trace was found in 29 per cent of his cases of intercapillary glomerulosclerosis. Here, again, mild or diffuse lesions may have been included in this series.

Available data concerning hypoproteinemia, hypercholesterolemia and edema are rather incomplete and vary considerably. Some of the earlier reports with relatively small series show rather high percentages. Newburger and Peters<sup>20</sup> and Porter and Walker<sup>21</sup> report the presence of significant albuminuria, hypoproteinemia and edema in 75 to 100 per

cent of cases. Hernandez Morales<sup>18</sup> reports a nephrotic picture in all of his 6 cases. Siegal and Allen<sup>8</sup> likewise stress the common occurrence of the nephrotic syndrome. In later large series, however, its occurrence is reported to be considerably less frequent. Goodfo<sup>3</sup> observed edema on a hypoproteinemic basis in 30 per cent of 18 cases with advanced lesions. Laipply<sup>4</sup> found that the nephrotic syndrome was present in only 6.3 per cent. Bell<sup>17</sup> states that only about a third of his cases showed edema and that in no case was it so marked as that in lipid nephrosis, 7.5 per cent. Grade 2 to 3 edema occurred in his cases of nodular intercapillary glomerulosclerosis. Henderson et al.<sup>16</sup> state that some degree of edema was present in 47 per cent of their cases of intercapillary glomerulosclerosis, but in only 6.6 per cent could the edema be classified as nephrotic in type. It seems justifiable to assume that with application of more rigid criteria, edema of the nephrotic type seems to occur in less than 10 per cent of cases of intercapillary glomerulosclerosis.

In summary, a significant degree of albuminuria occurs in the majority of cases of intercapillary glomerulosclerosis. The nephrotic syndrome, however, seems to occur in less than 10 per cent of the cases of intercapillary glomerulosclerosis verified by autopsy. It is of significance that no cases have been recorded of diabetes with nephrosis in which intercapillary glomerulosclerosis was not demonstrated.

#### (To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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### CASE 34251

#### PRESENTATION OF CASE

A sixty-three-year-old businessman entered the hospital because of persistent epigastric pain of eight months' duration.

Fifteen years and again five years before admission the patient had epigastric distress, which occurred following meals and also at night, awakening him from sleep. In both episodes the symptoms were relieved by food, milk and sodium bicarbonate. Eight months before admission he experienced similar but more severe epigastric distress and pain and did not respond to the usual regime. There was increasing anorexia, fatigue, lassitude and a weight loss of 20 pounds. The patient complained of generalized pruritus of two months' duration. He had had no jaundice or change in character of stools or urine. Unusual business and family problems existed during the period before he entered the hospital. An x-ray film of the gastrointestinal tract two weeks before admission showed the lower esophagus to be slightly wider than usual, and its folds were more prominent than usual, though not definitely tortuous. The proximal part of the stomach revealed no evidence of a filling defect, and peristalsis was normal. The pylorus and prepyloric region were spastic and narrowed throughout most of the examination but filled to a wide diameter at times and appeared distensible throughout. There was a suggestion of a small, constant accumulation of barium on the lesser curvature and antrum, which might have represented a small crater, mucosa appeared to be present in this region. The duodenal cap and loop were not remarkable. After six hours most of the barium lay in the terminal ileum and right colon, but there was a small residuum of barium mixture with fluid in the stomach. A qualitative test for sugar with Benedict's reagent was olive green. There was no bile or albumin in the urine. The red-cell count was 5,430,000 and the white-cell count 7600. After two weeks on a strict regimen for peptic ulcer the patient's symptoms were unrelieved. It was believed that he should be hospitalized in view of the x-ray findings to determine more clearly the nature of the lesion and to regulate his diabetes at the same time.

Physical examination showed a well nourished man with slight icterus of the scleras. A moderately firm, nontender lymph node 1 cm. in diameter was felt in the left axilla. The heart and lungs were negative.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood disclosed a hemoglobin of 14.4 gm. and a white-cell count of 12,900, with 76 per cent neutrophils. The urine had a specific gravity of 1.032 and gave a + test for albumin and a ++ test for bile, and the test for sugar was green. The sediment contained occasional pus cells. The fasting blood sugar was 171 mg., the phosphorus 3.0 mg. and the alkaline phosphatase 24 units per 100 cc. The serum bilirubin was 3.2 mg. per 100 cc. direct, and 4.0 mg. indirect. The fasting blood sugar on the second hospital day was 250 mg. per 100 cc. A gastric analysis revealed no free hydrochloric acid in the first specimen, but the third specimen contained 40 units of free acid, and the total acid was 51 units. The prothrombin time was 20 seconds (control, 21 seconds). The cephalin-flocculation test was negative. A stool was mustard colored.

An x-ray film showed the esophagus to be as before. The stomach was dilated and contained considerable fluid so that adequate examination was impossible. There was an area of irregularity in the prepyloric and antral regions. On the lesser curvature over a considerable distance, about 6 cm., was what appeared to be shortening of this portion of the stomach. It was not certain that there was a filling defect in this region. The second portion of the duodenum was narrowed, and there appeared to be pressure on its medial aspect. At the end of six hours most of the barium remained in the stomach, which was dilated.

Following admission to the hospital the patient became frankly jaundiced. He continued to have a great deal of epigastric pain, nausea without vomiting, and diarrhea. The pain was only partially relieved by milk and gelusil.

An operation was performed on the thirteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: This is going to be the shortest discussion on record, I hope.

"Unusual business and family problems existed." I looked at that statement with a good deal of skepticism because it appears to be trying to tell me that this man had an ulcer.

This patient had partial biliary obstruction. He had had it for some time. The fact that he itched, the fact that he had a measurable as well as an observable amount of icterus and that the alkaline phosphatase was considerably elevated means partial biliary obstruction. The common causes are

operative trauma (this patient had had no operation), stone in the common duct and tumor, especially tumor of the biliary tract or head of the pancreas. One other bit of evidence—this man had mild diabetes. It is my opinion that mild diabetes is commonly associated with chronic gall-bladder disease.

The question is, How are we going to decide whether this was tumor or stone? I am going to say that the patient had a stone in the common duct.

I must say one or two more things. Once in a blue moon one finds a peptic ulcer that will cause biliary obstruction. The ulcerative lesion is in the mid-portion of the duodenum, and in the cases that I have seen, the ulcers have been large. I do not want to insult the X-ray Department by telling them that this man had a large ulcer in the duodenum. It is stated that the duodenum was narrowed. Carcinoma of the pancreas is sometimes associated with widening of the duodenal loop. That is not mentioned here, but there was a suggestion of pressure on the medial side of the duodenum. From the report, that is the impression I got, which *should* lead one to the diagnosis of tumor.

There are various other exotic conditions such as xanthoma with obstruction of the biliary tract. Another rare situation is that of lymph-node involvement by tumor, with pressure on the bile duct and partial biliary obstruction. That is relatively rare, but I have to consider this lymph node in the axilla and I wondered if that might be part of a metastatic process. I cannot conceivably rule out a malignant process, and I have to put Dr. Wyman on the spot in just a moment because I am discounting some of these x-ray findings. For instance, stasis was marked on x-ray examination, but nothing is said in the record about clinical signs of stasis. There was no vomiting and no statement regarding intubation of the stomach, and it seems from the history that no one was impressed by this x-ray evidence of stasis. I get the impression that the x-ray findings were due to a change in motility. One can have changes in motility from biliary obstruction alone. The problem then is, Did this patient have carcinoma of the stomach with extension to give partial biliary obstruction? I will say before I see the x-ray films that I do not believe that he had carcinomas. The operation was a laparotomy, the stone was removed, and he was probably cured. May we see the x-ray films?

DR STANLEY M. WYMAN: The irregularity of the prepyloric and the antral regions is best seen in these two large films. The spot films did not show the lesion as we hoped they might. The area in question was flexible and distensible. The mucosa seemed to run throughout it. The duodenal cap filled out to a good normal contour and seemed to show no deformity or evidence of crater. The narrowing of the duodenum that is mentioned seems to be in the

second portion and seems to be somewhat changing in character. There is a suggestion of the so-called "inverted three" sign, which is often present in tumor. This was not definite. We concluded that the patient had pressure on the medial aspect of the second portion of the duodenum and that he had disease in the prepylorus, which was perhaps old and represented scarring. There seemed to be no evidence of infiltration of the second portion of the duodenum, and this was considered a purely extrinsic pressure manifestation.

DR RICHARDSON: That was fairly definite though?

DR WYMAN: Yes, it seemed definite.

DR RICHARDSON: It shows what seems to be pressure.

DR WYMAN: It is not widened, though. The loop does not seem increased in size on that film. On this film it is larger than usual, and the second portion of the duodenum seems to lie more toward the right than one would expect. This is a six-hour film at the second examination, showing considerable retention of barium in the stomach.

DR RICHARDSON: I cannot laugh off this lesion in the prepyloric region. It must be an intrinsic lesion.

DR WYMAN: I believe so. My own impression was that it was a scar due to a previous ulcer.

DR RICHARDSON: I have to take that lesion in the stomach seriously, and it may well account for the stasis. I am not sure how seriously to take the duodenal lesion. If one takes it really seriously, it is evidence in favor of tumor. I do not see how it could have been an ulcer of the midportion of the duodenum with biliary obstruction. I will say that the patient had, in addition to stone, a benign gastric ulcer, since he had a history of epigastric pain going over fourteen years or more—a long period.

I shall summarize, then, by saying that he had a stone in the common duct and benign gastric ulcer, perhaps healed at the moment, with a good deal of scarring, and I do not know what he had in the duodenum. What do you say, Dr. Adams?

DR F. DENNETTE ADAMS: I would put my money on tumor.

DR RICHARDSON: Where?

DR ADAMS: During the last fifteen minutes I fluctuated from pylorus to pancreas. In view of the fact that some relief from pain was afforded by a Sippy diet, I would put it in the pylorus.

DR WYMAN: What about stones?

DR ADAMS: I do not believe that the history is consistent with stones.

DR RICHARDSON: I thought perhaps on the law of chance that tumor would be more likely, but I will stick to stone in the common duct, and I believe that the operation was a laparotomy. It may have been a lymph-node biopsy from the right axilla,



which turned out to reveal a reticulum-cell sarcoma, or the operation may have been a gastroscopy. Do you still do that to us, Dr. Mallory?

DR. TRACY B. MALLORY: It was a laparotomy.

DR. ADAMS: One more statement—if this man had trouble from a stone in the common duct, he should have had some fever, I believe.

DR. RICHARDSON: He may have had. We had one extraordinary patient on the ward with itching of a year's duration and no fever who was operated on and a stone was found in the common duct.

DR. ADAMS: This man had so much jaundice and so much obstruction that he should have had fever.

DR. RICHARDSON: One had better say that the diabetes was incidental. Diabetes associated with carcinoma of the pancreas appears very late in the disease.

DR. ADAMS: That would be rare.

DR. RICHARDSON: Incidental diabetes goes better with disease of the gall bladder.

MR. GEORGE A. McLEMORE, JR.: How about diabetes with chronic pancreatitis?

DR. RICHARDSON: That would be in favor of stone.

DR. DANIEL S. ELLIS: This patient was first seen two weeks before admission to the hospital. The course at that time seemed perfectly typical of peptic ulcer, though the history of itching bothered me a little. When I found sugar in the urine I took it to be due to diabetes. The first x-ray film was reported as showing the presence of probable ulcer in the prepyloric region. In two weeks, between the time he was first seen and when he came back for x-ray and follow-up study, the patient had not had any relief on a strict ulcer regime, and he had continued to lose weight. He was admitted to the hospital because we thought he had a lesion in the stomach that probably should come out. We also hoped to find out more about the diabetic setup. He was not jaundiced, and he had no bile in the urine. As a matter of fact, the jaundice was not detected until two days after admission to the hospital, when he became frankly jaundiced, but he had bile in the urine. X-ray examination was repeated, and Dr. Wyman has described the findings. We also thought that he had involvement of the stomach, probably cancer of the stomach involving the pancreas or cancer of the head of the pancreas involving the stomach. As an outside possibility we hoped that this man had a chronic ulcer that had perforated into the head of the pancreas and caused a large inflammatory mass, which might have accounted for the pressure defect seen on the duodenum.

#### CLINICAL DIAGNOSIS

Carcinoma of head of pancreas?

DR. RICHARDSON'S DIAGNOSES

Stone in common bile duct

Gastric ulcer, ? healed

#### ANATOMICAL DIAGNOSIS

*Adenocarcinoma of common bile duct and papilla of Vater.*

#### PATHOLOGICAL DISCUSSION

DR. ELLIS: Dr. McKittrick explored the patient. The first surprise was that the stomach was entirely normal, perfectly free and fairly movable. There was no evidence of new or old ulcer that one could see or feel in the stomach or in the duodenal cap. We were a bit perplexed, and Dr. McKittrick explored the head of the pancreas, which felt perfectly normal. He tried to free up the duodenum, and in the second portion of the duodenum, before it was opened, there appeared to be a soft, movable mass, about the size of a man's thumb. The duodenum was then opened longitudinally, and for the moment it was difficult to visualize a mass. Subsequently, on the posterior wall, at the ampulla of Vater, an intramural mass was found, which seemed to involve the common duct. It was obviously a tumor involving the distal end of the common duct where it runs through the wall of the duodenum. The question was whether or not a radical resection and Whipple type of operation were to be done—or whether a local excision might be successful. Dr. McKittrick finally decided to attempt a local excision. He transected the duodenum and resected a segment about 5 cm in length, which included the papilla and portions of the common bile duct and the duct of Wirsung. He sewed the severed ends of the common duct and the pancreatic duct into the posterior wall of the duodenum and then made an end-to-end anastomosis.

DR. MALLORY: The specimen that we received was a segmental resection of the duodenum with the papilla of Vater in the center. The papilla was occupied by a tumor that proved to be a very well differentiated adenocarcinoma. A portion of the tumor was relatively benign in appearance, and another portion definitely invasive and malignant, suggesting that the tumor started as a benign polyp and later became malignant. Both polyps and carcinoma can occur in the ampulla of Vater.

DR. RICHARDSON: This does not sound as if it would account for the narrowing of the duodenum.

DR. ELLIS: It would have presented a defect in the lumen of the duodenum. There was no way that it would account for narrowing by compression from outside.

DR. ADAMS: How is the patient doing?

DR. ELLIS: The postoperative course was interesting. For three days it was excellent, but during the next twenty days he had a stormy time. A T-tube had been sutured into the common duct, and a cigarette drain in the foramen of Winslow. For the first few days the patient drained 700 cc of normal bile, then the wound began to drain copious quantities of bile-stained material, between

2200 and 2500 cc a day. With this much loss of fluids we were unable to keep the electrolyte or the nutritional balance. The chloride fell to around 83 milliequiv per liter, the nonprotein nitrogen rose steadily to 125 mg per 100 cc, and he became uremic and began to lose ground. Needless to say we became very worried about him. About a week postoperatively, we decided that we had to do a jejunostomy to feed him because anything we gave by mouth was coming out through the common duct. Almost as soon as jejunostomy was done, he improved, and whether it was time for him to get well or whether the procedure accounted for it we could not decide. We were able to feed him back the contents of the common-duct-tube drainage. The nonprotein nitrogen fell to normal within three or four days. The diabetes, which had been something of a problem immediately postoperatively, cleared up in time. At the end of about two months we sent him home. I talked to him yesterday and he has gained 5 pounds, is walking around and wants to go back to work.

A PHYSICIAN: Was the stomach opened?

DR ELLIS: No.

DR RICHARDSON: Therefore, a healed gastric ulcer has not completely been ruled out.

## CASE 34252

### PRESENTATION OF CASE

An eighty-one-year-old retired policeman was admitted to the hospital complaining of a mass in the neck and fever.

He had been in exceptionally good health all his life until six months before admission, when he noted a nontender area of swelling in the left side of the neck. The mass gradually increased in size and was noted by his family for the first time one month before admission. During the three weeks preceding admission it increased rapidly and he was aware of a shift in position of the hyoid bone as though his "windpipe were broken." Four days before admission he had a severe shaking chill followed by fever and marked weakness. There were no subsequent chills, but the fever continued until admission.

He had had mild dyspnea on exertion for several years and slight ankle edema but no orthopnea or hypertension.

Physical examination showed an obese man appearing much younger than his stated age. The fundi were normal. The posterior pharyngeal wall was slightly injected. No masses were visible inside the mouth. The neck was short and thick. A nontender mass, measuring 9 by 9 cm, occupied the left side of the neck, its upper and lower margins seemed to be bounded by fascial planes. Some observers believed it to be solid, others thought it was cystic. The trachea and the hyoid bone were

deviated to the right. The heart was questionably enlarged. The rate was grossly irregular at 110. No murmurs were heard. Scattered coarse rales were heard at the lung bases bilaterally. No organs or masses were palpable in the abdomen. The prostate was firm and enlarged to two and a half times the normal size.

The temperature was 102.2°F. The blood pressure was 110 systolic, 80 diastolic.

Examination of the blood demonstrated a hemoglobin of 14 gm and a white-cell count of 14,500, with 85 per cent neutrophils. The urine was not remarkable. The stools were guaiac negative. The nonprotein nitrogen was 41 mg and the total pro-



FIGURE 1

tein 62 gm per 100 cc. An electrocardiogram showed auricular fibrillation, with a ventricular rate of 95, and no other definite abnormality.

On x-ray examination the esophagus was found to be markedly displaced to the right and also somewhat anteriorly. There was no evidence of intrinsic involvement of the proximal esophagus. The mediastinum showed considerable widening, both superiorly and at the level of the hilar structures (Fig 1). X-ray examination of the nasopharynx and the base of the skull showed no abnormalities. The basal metabolic rate was -15 per cent.

During the first three hospital days the temperature gradually reached normal levels. On a low-salt diet and digitalis the respiratory symptoms subsided.

An operation on the neck tumor was performed.

## DIFFERENTIAL DIAGNOSIS

DR IRAD B HARDY May we see the x-ray films?

DR JAMES J McCORT These films show the mass described on the left side of the neck, displacing the trachea and the esophagus markedly to the right. A small amount of barium remains in the pyriform sinuses. The mediastinum is wide and continues so to about the level of the aortic arch. There seems to be a definite soft-tissue mass lying in this region. The heart is slightly prominent in the region of the left ventricle. The aorta is tortuous. A spot film taken of the barium in the esophagus shows the marked displacement described to the right and anteriorly.

DR HARDY Is there any calcification or any irregularity in the soft-tissue mass?

DR McCORT It seems to be smooth, and there is no calcification in it.

DR HARDY In summary, we have an eighty-one-year-old man who was essentially well until six months before he entered the hospital. At that time he noticed a gradually increasing mass in the left side of the neck, which was first noticed by the family one month before entry. It appeared to increase more rapidly in size over the three weeks immediately preceding entry, and a few days before he arrived in the hospital he had fever and a chill. Apparently he had no true obstructive symptoms from the mass. He had some cardiac symptoms that could be explained on the basis of the heart alone, I suppose, without obstruction.

So far as the physical examination is concerned, we find only a few points in the abstract that were abnormal. The mass in the neck is described as measuring 9 by 9 cm, it was nontender. Outside that there is nothing to help us. We would like to know whether it was freely movable or attached to the skin or more movable laterally than up and down—whether there was a bruit or any pulsatile qualities to the mass.

DR TRACY B MALLORY Dr Aub, can you answer any of those questions?

DR JOSEPH AUB The mass was rubbery, had a smooth edge and was enormous. It could be felt up and down the neck and deep into the mediastinum.

DR HARDY The patient was fibrillating. I assume, however, that that was incidental and was on the basis of arteriosclerotic heart disease. The prostate was two and a half times the normal size. He had had no genitourinary symptoms. I suppose he was entitled to that much enlargement at eighty-one years of age, it was probably benign hypertrophy.

Perhaps some of you could come out with a diagnosis now, but for me to try to make a working diagnosis it was necessary to go through the differential diagnosis of lumps in the neck. I still do not know whether I can make a diagnosis. We

might mention some of the possibilities purely to exclude them, I hope. In the first place, I thought of the so-called congenital lesions. A man of eighty-one is rather old for an initial appearance of these cystic structures, but there certainly are rare cases in which congenital cysts have appeared late in life, in middle age anyway. Branchial-cleft cysts occur and may occasionally degenerate into carcinoma. The cystic hygromas—the types of tumors that arise from lymph tissues—certainly appear most frequently in younger people, and I think they are usually lower in the neck, probably supraclavicular in most cases, the supraclavicular part being the largest part of the tumor. The thyroglossal cyst is midline, this was definitely lateral. I believe that the congenital types of lesion can be excluded, principally because of the patient's age.

We next should consider the infections—the involvement of the lymph tissue from infection, both acute and chronic, specific and nonspecific. I think that any acute lymphadenitis of this size would have been associated at an earlier date with more systemic symptoms of infection and that the lymph nodes would have been tender. It is definitely stated that this mass had never been tender. So far as the specific types of lymphadenopathy are concerned—for instance, tuberculosis—it would be most unusual for the first indication to appear at this age. Also, the size of the mass is very much against that particular type of pathologic process.

In passing, we must think of the so-called lateral aberrant thyroid tissue and possibly of cancer. The mass developed rather rapidly in size for such a lesion, however, and was probably much larger than one sees in that disease.

The fact that the patient was eighty-one and that in the transcript there was mention of widening of the mediastinum might make one wonder if this man had some type of aneurysm of one of the great vessels in the neck, such as the carotid. But there were no pulsations, the mass was not pulsatile. I think at that age an aneurysm would have had some calcification in its walls. Also, the widening of the mediastinum does not appear to have been aneurysmal in character. The aorta was somewhat dilated but probably consistent with his age.

That, to me, leads down to various tumors that can occur in this area. I should think that the growth was too rapid to consider the benign type of tumors that can occur in this area and reach good size. It could have been an enormous lipoma, but the soft-tissue shadow of lipoma is more or less pathognomonic. I believe that the systemic symptoms and the rapidity of the growth are against that diagnosis. The patient probably could have had a mixed tumor of one of the salivary glands, either the submaxillary or, less likely, the parotid. There again the rapidity of growth is

against a benign tumor. There are tumors of the carotid body, but if the mass in this case were such a tumor it would have been the largest one on record.

There are several things against the diagnosis of leukemia. Of course, the fairly well localized character of the lesion, the normal blood picture and, I suppose, the age are against that.

Metastatic carcinoma is certainly one of the more common conditions that we ought to consider in this age group. From the record it is my opinion that the growth, if the family first noticed it three weeks before entry, was too rapid for a metastatic carcinoma, and some studies were done to try to find a focus for the primary growth without success. The nasopharynx was normal, nothing was visible inside the mouth, and the stools gave a negative guaiac reaction — apparently the gastrointestinal tract was normal. The chest film, so far as the lungs were concerned, was also normal.

There are such weird tumors as the various types of sarcomas — fibrosarcoma, fibromyxosarcoma or something of that nature. I believe that the rapidity of growth and size are consistent with that type of lesion. I should think, without knowing the statistics exactly and having put a good deal of weight on the stated appearance of the mediastinum by the x-ray study, in which the hilar structures as well as the rest of the mediastinum superiorly were mentioned, that this represents probably a lymphosarcoma with some mediastinal-lymph-node involvement — the greatest amount of disease being in the location of the mass as described. The more I look at the film, however, the more I am impressed by the fact that this may have been some kind of huge tumor involving the left side of the thyroid gland, but I had not considered that too strongly beforehand and I think I will stick to the diagnosis of lymphosarcoma with some degeneration and softening in the late stages so that the question of whether or not it was cystic or solid was raised. Also, that would be enough to explain the rather recent fever and chills that this patient had.

Dr. McCORT: Did the mass move on swallowing?

Dr. AUB: As I remember, it did. It was a big tumor that pushed the trachea over so far that we thought the patient would suffocate. It extended downward from the jaw into the mediastinum. My recollection is that it moved with swallowing.

Dr. HARDY: That would favor some lesion of the thyroid gland.

Dr. McCORT: That is what I had in mind. In a short-necked person any deep tumor of the neck is apt to extend down to the superior mediastinum.

A PHYSICIAN: Was the tumor fixed to the skin?

Dr. AUB: No, it was not fixed.

Dr. MALLORY: Have you anything to add, Dr. Aub?

Dr. AUB: I am here because someone told me that I made a terrible error in this case. I do not believe that it was so serious after all. We arrived at the same conclusion as Dr. Hardy that some form of lymphoma was most probable, but we could not rule out a cyst and so thought it would be wise to stick in a needle. That is about what Dr. Hardy thought.

#### CLINICAL DIAGNOSIS

Malignant lymphoma?

Cyst of thyroid gland?

#### DR. HARDY'S DIAGNOSIS

Lymphosarcoma of cervical and mediastinal lymph nodes

#### ANATOMICAL DIAGNOSIS

*Colloid goiter, with cyst formation*

#### PATHOLOGICAL DISCUSSION

Dr. MALLORY: The mass was aspirated, and fluid very readily obtained. A minute biopsy was obtained at the same time, which showed a small amount of quite distorted granular tissue suggesting thyroid. Following that the patient was prepared for operation, and a large colloid goiter with extensive secondary cyst formation within it was successfully dissected.

Dr. ALFRED KRANES: What was the reason for the chills and fever? Was there any necrosis?

Dr. MALLORY: There was no very acute necrosis that we could see. He had had beta-hemolytic streptococci in his throat at one time.

Dr. KRANES: The febrile episode may have been independent.

Dr. McCORT: How do you explain the rapid growth?

Dr. MALLORY: Ordinarily, that is explained on the basis of hemorrhage and then secondary degeneration of the blood clot. However, the aspirated fluid was clear, not hemorrhagic, so that I have no good explanation. Growth must have been due to a rapid accumulation of fluid. There was nothing to indicate rapid growth in any of the solid tissue.

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## TYPHUS FEVER IN BOSTON

ELSEWHERE in this issue of the *Journal* there is a report of 2 cases of typhus fever occurring in persons who have lived in Boston for many years. These cases should serve to call attention to the fact that typhus fever may be encountered in this vicinity from time to time. They also illustrate some interesting clinical and epidemiologic features of the disease and bring out some of the recent advances in the methods of more precise serologic diagnosis in the group of rickettsial infections.

Of particular interest is the fact that in both cases the clinical features, including the physical

and x-ray findings, were consistent with a diagnosis of the so-called primary atypical or "viral" pneumonia. Typhoid fever or some rickettsial infection was suspected only after the appearance of a rash. The fact that bacteriologic and serologic findings were negative for typhoid fever led to the serologic studies upon which the diagnosis of typhus fever was eventually established, first by the Weil-Felix reaction and finally by the tests for specific antibodies against the typhus rickettsias.

From an epidemiologic point of view the possible source of infection in these cases is of considerable importance. Both were isolated cases in which louse-borne infection seemed very unlikely. Nevertheless the results of the serologic tests indicated that the disease was indeed caused by the epidemic or louse-borne strain and not by the murine type of typhus rickettsia. It was then readily determined that both patients had immigrated many years ago from a part of Ireland where louse-borne typhus has been known to occur in epidemics from time to time in recent years. It was particularly significant that such epidemics had been recorded in the same area at the time when these patients were children and were still living there. These cases are thus brought within the group of infections usually known as Brill's disease.

These 2 cases should stimulate further discussion of Zinsser's hypothesis of the etiology of Brill's disease. Zinsser suggested that the mild typhus fever among immigrants from areas where classic typhus has occurred in the past represents a recrudescence of classic typhus many years after the initial attack. Serologic evidence supports this view, but proof must await the isolation and complete characterization of the strains of typhus from cases of Brill's disease. Such a study is currently in progress in the Rickettsial Disease Laboratory of the Harvard School of Public Health. It is hoped that clinicians who encounter suspected cases of Brill's disease will communicate with the Laboratory so that strain isolation may be undertaken, particularly in the first week of a patient's illness.

## WOTTON AND TRUETA ON SERVET

WILLIAM WOTTON was a child prodigy. By the age of five he could read the Bible in Latin, and when he was six no less a person than Sir Thomas Browne heard him read in English, Latin, Greek and Hebrew, "and construed the same truly." He entered Cambridge University at ten and graduated B.A. in 1679 at the age of thirteen. After a fellowship at St. John's College, Cambridge, he graduated M.A. when seventeen and was elected a fellow of the Royal Society in 1687, at the age of only twenty-one. In 1691 he was made a bachelor of divinity, and although he became a chaplain and later a rector, Wotton's chief contributions were literary. One book, published before he was thirty, made his name known to all historians, and medicine in particular is profoundly indebted to him for his *Reflections upon Ancient and Modern Learning*, first issued in 1694. It was in this book that Wotton called attention for the first time to Servet's description of the lesser or pulmonary circulation. The book itself, moreover, is remarkable, especially for a product of the seventeenth century, for it is chiefly devoted to the clear statement of facts. Wotton's *Reflections* is the best summary of the discoveries in nature and in physical science up to the time of its publication. A second edition was printed with additions in 1697, and a third in 1705.

The important notes on Michael Servetus, Spanish physician who was burnt at the stake on Calvin's orders in Geneva in 1553, were taken by Wotton from a copy of the passage in the *Christianismi Restitutio* furnished to him by Charles Bernard, a learned surgeon of London. Wotton never saw a copy of Servet's book. As we now know, only three of the one thousand printed copies, issued in 1553, are definitely known to have survived the fire. Servet, as pointed out by Wotton<sup>2</sup> in 1694, "clearly asserts, that the blood passes through the lungs, from the left to the right ventricle of the heart, and not through the partition which divides the two ventricles, as was at that time commonly believed." In addition, Servet anticipated Harvey in suggesting, but not confirming, the general circulation of the blood.

Thus Wotton, the scholarly divine, brought to the notice of the medical world the discovery of the pulmonary circulation.

Two hundred and fifty years have passed since Wotton's book was published. Much has been added to our knowledge of the Spanish physician and the life that he led in the passing years by biographers such as Allwoerden, Willis, Tollin, Gordon, Ward and Gener. The speeches for the prosecution and for the defense at the Geneva trial, among the most dramatic documents in the history of mankind have been published. More recently, Trueta,<sup>3</sup> a learned Catalonian surgeon, formerly in Barcelona but now at Oxford in England, has reviewed the life of Servet in a pleasant small book, *The Spirit of Catalonia*. He points out that Miquel Servet, to give him his Spanish name, born in 1511, even as a student in Barcelona showed a frankness and passionate love of free thought that got him into immediate trouble. He was shipped off to Toulouse and then to Italy, to Bologna and Padua, to Germany and elsewhere. He soon expressed heresies—on the nature of the Trinity and on the existence of the Son of God as a real man. After publication in 1531 of his first book, *De Trinitatis Erroribus*, he had escaped to France. Indeed much of his whole short life was one of fleeing from persecution. He managed to study anatomy in Paris, with Sylvius, Fernel and others, along with his fellow pupil, Vesalius Gunterius, the anatomist, praises both Vesal and Servet, who acted as his preceptors.

When danger came to Servet in Paris, because of his religious views and his outspoken manner, he went to Vienna, where he remained for twelve peaceful years as physician to a Cardinal. Here he arranged and edited an edition of the Bible, disclosing a wide knowledge on the most varied subjects of theology, history and natural science. It was in Vienna also that he wrote his greatest work, the *Christianismi Restitutio*. The manuscript, dated 1546, has also by chance been preserved and is now in the National Library of Paris.

In the light of present knowledge, how much credit should go to Servet for his clear insight into the great error? His book of 1553 hardly merits the construction, those of Valverde (1553) and

and Columbus (1559) both advancing the same theory of the circulation through the lungs, fared better Harvey knew of Columbus, but not of Servet, and to Harvey goes the honor of the greater discovery Servet's place in history, however, is secure, and is made more so by his fellow countryman, Trueta

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### ADOPTION IN MASSACHUSETTS

A COMMUNICATION published elsewhere in this issue of the *Journal* calls attention to a problem with which most physicians are familiar the adoption of the illegitimate child The increase in illegitimate births in recent years seems to justify the conclusion that the problem will be present for many years to come, and in recognition of that fact, adoption laws in the Commonwealth have been under investigation by a commission that is expected to make recommendations for necessary revisions at this session of the Legislature

It is reassuring that a private organization such as the Boston Children's Friend Society continues to do its utmost to solve the problem of adoption Few decisions require more tact and skill than the suitable placing of a child unwanted under one roof, so badly wanted under another The ultimate welfare of the child is the primary consideration, but attention must also be given to the rights and feelings not only of the childless couple, who after having become attached to a child are sometimes forced to give him up, but also of the mother, who under the pressure of circumstances beyond her control may relinquish her child and later regret the step bitterly The Boston Children's Friend Society, through the efforts of specially trained workers, attempts to place these children in appropriate homes and also to make sure that the adoption will be permanent The child is given a complete examination, including physical, x-ray and psychologic study, and is placed in a boarding home for three or four

months before adoption Thus, there is sufficient opportunity for judging his physical and mental character, and the mother is given time to be certain that she wishes the child to be placed with a suitable family, the adopting parents are consequently spared the threat of litigation and possible removal of the child in the years when they have become most attached to him

The activities of the Boston Children's Friend Society merit the highest commendation every effort to ensure suitable and permanent homes for these children, and to enable them to grow up as self-respecting citizens of the community, should have the fullest co-operation and support of all elements of society

### MORTALITY OF INSURED INFANTS

INFANT mortality rates for the first year of life have been unusually low in recent years, according to a report made before the annual meeting of the Actuarial Society of America by Richard J Learson, vice-president of the Western and Southern Life Insurance Company of Cincinnati

Of particular interest is the observation that the death rate among insured infants has been only one third of the general infant death rate for the country as a whole Apparently we take especial care of that which we prize highly enough to insure Actuarial studies have shown further that infant mortality rates at all social and economic levels in the cities are lower than those in outlying regions

Pneumonia is listed as the leading cause of death, with congenital defects, debility and prematurity coming next, and diarrhea and enteritis third These three causes account for nearly 60 per cent of all the deaths under one year of age Obviously, much can still be done to preserve life at its beginning as well as to prolong it at its end

### MASSACHUSETTS MEDICAL SOCIETY DEATH

ST DENIS — J Nelson St Denis, M.D., of Roslindale, died on May 20 He was in his eighty-third year Dr St Denis received his degree from Baltimore University School of Medicine in 1892 His widow and five brothers survive

## MISCELLANY

### VETERANS ADMINISTRATION APPOINTMENT

Dr. William Reid Morrison, of Boston has been appointed chief consultant for surgery of the Veterans Administration. Dr. Morrison, a founder of the American Board of Surgery has been associate and clinical professor of surgery Boston University School of Medicine and surgeon in-chief of the first surgical service at Boston City Hospital.

## CORRESPONDENCE

### ADOPTION

To the Editor The adoption of the illegitimate child and the care of the unmarried mother are sometimes troublesome and baffling problems to the practicing doctor. It may be of interest to the physicians of this area to know that the Boston Children's Friend Society, which has been serving the children of the community for one hundred and fifteen years, has recently enlarged its adoption service. The child is placed for adoption by specially skilled workers who match the background and capacity of the infant and adopting parents and arrange suitable boarding care for the unmarried mother when needed.

Inquiries may be addressed to the general secretary Boston Children's Friend Society 123 Marlborough Street, Boston 16, Massachusetts.

HAZEL S. MORRISON, General Secretary

Boston Children's Friend Society

### CAUSE OF ELEVATED CEREBROSPINAL-FLUID SUGAR

To the Editor I am a loyal follower of your Journal and I believe I learn a lot from its contents. I wish to express my thanks, but also to point out an error appearing in my last number.

In the Case Records of the Massachusetts General Hospital (Case 34201) in the issue of May 13, Dr. Raymond D. Adams made the following statement "Elevated cerebrospinal fluid sugar is always [italics mine] related to a high blood sugar, either from diabetes mellitus or, as in this case, with no glycosuria from injection of glucose intravenously."

Using the text by Cantarow and Trumper as an authority, I would like to dispute this statement. This text lists as causes of hyperglycemia such diseases as syphilis of the central nervous system and increased intracranial pressure.

I presume that the misunderstanding is due to incorrect expression.

GLENN M. MORRIS, M.D., Assistant Resident Physician

The Norwegian Lutheran Deaconesses Home and Hospital Brooklyn, New York

Dr. Morris's letter was referred to Dr. Adams whose comment is as follows:

To the Editor The present opinion in most neurologic clinics is that the cerebrospinal fluid sugar closely parallels the level of blood sugar being elevated when the blood sugar is elevated and lowered when the blood sugar is lowered. The only exception to this is when bacteria or fungi are present in the cerebrospinal fluid. It follows from these facts, therefore, that one would expect the cerebrospinal fluid sugar to be elevated in untreated diabetes after a large dose of intravenous glucose and exceptionally when the walls of the third ventricle are damaged, as in a massive brain hemorrhage or other acute lesions in the same area. Certainly in our experience syphilis has no significant effect on the cerebrospinal fluid sugar nor does increased intracranial pressure.

RAYMOND D. ADAMS, M.D.

### DIAGNOSTIC PERICARDIAL TAPS

To the Editor From my hospital experience dating from 1910 I have observed that members of the medical staff in particular, are overcautious about performing diagnostic pericardial taps. They seem to be as fearful of resorting to that procedure as my teachers were about the aspiration of the knee joint. Today with the aid of x-ray films taken from different points and using both the recumbent and erect

positions it is quite unnecessary to wait for the development of the classic signs of pericarditis with effusion.

The actual danger of this simple test is insignificant. During my internship house officers could obtain the necessary rabbit serum for the prevailing treatment of certain hemorrhagic diseases only by aspirating blood from the hearts of the animals, appropriately anesthetized without especially suitable needles. In spite of the relatively small ventricles of the rabbit's heart, we were, with rare exception successful in withdrawing the usual amount of blood without the untoward death of the animal.

Paracentesis of the distended pericardium is not only of unique diagnostic value but also a prognostic and therapeutic aid both direct and indirect. With needles of a bevel no greater than that needed to penetrate the pericardium and with the choice of a site near the apex of the heart, there should be no incidental danger and no shock.

It is high time to dispel this bogey.

G. W. HAIGH, M.D.

242 Burncoat Street  
Worcester Massachusetts

### RH DETERMINATION A PUBLIC HEALTH FUNCTION?

To the Editor The editorial entitled "Threatened Curtailment of State Services" which appeared in the March 25 issue of the Journal and which recommended continued determination of Rh factor by the Department of Public Health has caused great concern and amazement among pathologists in and outside Massachusetts.

The editorial supports the concept of increasing socialization of medicine in one particular field of medical practice and encourages the invasion of the field of clinical pathology by state-supported laboratories. This tendency threatens the existence of the pathologist as a medical specialist; creates an uncertainty for the future of this branch of medicine and deters young graduates from specializing in it.

The determination of the Rh factor is a laboratory procedure that does not properly fall within the scope of a public health laboratory. Such determinations are now being capably performed in hospital and private laboratories throughout the Commonwealth under the supervision of pathologists. Potent and reliable antiserums are freely available; the technique is standardized and the determination by a trained technician is as accurate as an ordinary blood grouping. When special techniques or less commonly available antiserums are required recourse to freely accessible larger laboratories can readily solve the problems.

Although charges are properly made for the Rh determination in private and hospital laboratories, the pathologist recognizes his obligations to the patient and the test is done without charge whenever necessary.

The pathologist is peculiarly vulnerable to the inroads of socialized medicine. His future, however, is intimately related to that of all practicing physicians and invasions of his province should arouse the concern and support of the medical profession.

D. A. NICKERSON, M.D.

Salem Hospital  
Salem, Massachusetts

The changing concepts of what does and what does not constitute legitimate public health procedure have long been a subject of debate. All physicians will doubtless agree that the basic factor is the care of the patient. All opinion must eventually pass through this filter. — En

### DR. AUGUSTUS S. KNIGHT

To the Editor Dr. Augustus Smith Knight, Harvard A.B. 1887 and M.D. 1891 died in the Somerset Hospital, Somerville, New Jersey on March 21, 1948, after injuries received in an automobile collision. He was eighty-three years of age. Dr. Knight, who was born in Manchester, Massachusetts, received his early education in the public schools and at Phillips Andover Academy. He was popular as a student and generally liked by all who came in contact with him during his college years and afterward. He served as medical house officer at the Boston City Hospital in 1890 and 1891.

After graduation from Harvard Medical School he engaged in the practice of medicine at 1 Exeter Street, Boston and received an appointment as medical examiner in Boston for the Metropolitan Life Insurance Company of New York.



He was soon invited to New York as a subordinate examiner and here remained in the service to which he was so peculiarly adapted. His advance continued steadily until he was appointed medical director and a vice-president of the Company, remaining in the service until his retirement in 1934.

Dr Knight was also active in medical affairs in New Jersey, where he resided, and held affiliation with hospitals and important medical societies.

Dr Knight's first wife was his cousin, the former Abbie Knight, who died in 1929.

He is survived by his second wife, Anita Merle-Smith, to whom he was married in 1930, and by their son, Augustus S Knight, Jr.

He placed many younger doctors from Boston and the City Hospital in service for the Metropolitan Life Insurance Company in New York and elsewhere. To the writer of this note it is a most pleasant recollection to review his acquaintance and association with Gus Knight, particularly the memory of two summer months in 1890, when as medical students they lived together in harmonious service, gaining practical instruction in obstetrics in the outpatient department of the Boston Lying-in Hospital.

JOHN L. AMES, M.D.

Larchmont  
New York

## BOOK REVIEWS

*The Psycho-Analytical Approach to Juvenile Delinquency Theory case-studies treatment* By Kate Friedlander, M.D. (Berlin), L.R.C.P., L.R.C.S. (Edin.), D.P.M. (London), 8°, cloth, 296 pp. New York: International Universities Press, 1947. \$5.50.

On the premise that the fields of psychology, criminology and penology, and sociology have lacked co-ordination in their attempts to solve the problem of juvenile delinquency, the author aims to show the types of patients who can be aided by psychoanalysis with the combined co-operation in research by these scientific groups. The book is divided into three parts: factors responsible for the social adaptation of all persons, including the child's early relationship to his mother, the Oedipus conflict, the super-ego formation and group formation inside the family, the interaction of the state of "latent delinquency" with the various experiences discussed in the first part, which may lead to delinquent behavior, and the author's classification of juvenile delinquency as antisocial character formation, organic disturbances and psychotic ego-disturbance, and treatment and material on prevention and education of field workers. The treatment that is discussed as psychologic (psychoanalytic) is useful in handling patients with antisocial character formation and organic disturbances, and the environmental aspect is particularly necessary when delinquent behavior is due to antisocial character formation and when the home is "beyond repair." The author, in conclusion, summarizes a rational scheme for the prevention of crime, including abolition of factors leading to antisocial character formation with measures to be taken in the schools and after the school age, as well as when the young person comes before the court. This book should be of interest to all workers in the field of juvenile delinquency, although the psychoanalytic approach as yet is neither concrete nor expeditious enough to have very wide application. Each section of the book has a rich bibliography, and the case material is extensive, pertinent and well expressed.

*Ear, Nose and Throat Symptoms-diagnosis-treatment* By George D. Wolf, M.D. 8°, cloth, 523 pp., with 149 illustrations. Philadelphia: J. B. Lippincott Company, 1947. \$10.00.

The author attempts to present the common ailments of the ear, nose and throat by a classification of otolaryngologic symptoms. This modern presentation affords the student a very readable text printed on fine paper, in large print and well spaced. The approach shows the author's effort to fall in line with the current teaching emphasis on the symptomatic history as a most important aid in arriving at a diagnosis. However, the book demonstrates that it is quite impossible to execute his purpose. The text describes the physical findings quite accurately and lucidly and is similar

in content to other recent practical small editions on diseases of the ear, nose and throat. Certain specific statements made by the author are certainly open to criticism, examples of which are the following: "he [the author] has not encountered post-tonsillectomy bleeding if no aspirin is used" and "in the treatment of lateral sinus thrombosis, first ligate the jugular vein."

The many clear and self-explanatory sketches taken from Dr. Lyman Richards's textbook, *Otolaryngology in General Practice*, are excellent and of much aid in the material presentation.

The author briefly introduces the student and practitioner to otolastic and rhinoplastic procedures. Details are necessarily omitted in a compact volume such as this book is intended to be. The reference to endoscopy is also brief.

At the end of the book there are chapters on barotrauma and antibiotic therapy and, as a final chapter, the equipping of an otologist's office. A very liberal bibliography of current otolaryngologic literature has been utilized to bring the material up to date, and medical therapy is well covered.

*Medicine for Moderns The new science of psychosomatic medicine* By Frank G. Slaughter, M.D. 8°, cloth, 246 pp. New York: Julian Messner, Incorporated, 1947. \$3.50.

This is another medical book designed for the layman. The author is a well known novelist, in addition to being a well recognized surgeon. The reader can expect, therefore, interesting and dramatic presentation of the subject.

The volume is educational and attractively written. To mention only a few of the twenty-six chapters, particular attention is called to the following: "The Case of the Blushing Stomach," which describes the patient with peptic ulcer, "The Discontented Colon," which describes colitis and spastic colon, "Coronary Thrombosis The price of success" which correlates the disease and the personality, "My Love is Rosy Red," explaining the skin manifestations of emotions, and "The Reluctant Lover," which deals with repressions, frigidity, impotence and sexual deviation. Dr. Slaughter is a brave author, even to the extent of calling a chapter on socialized medicine "Revolution in Medicine."

No reader will agree with all his ideas. The reviewer notes the following contradictory statements: "This is the story of the new science of psychosomatic medicine" (Page 2), "Hippocrates undoubtedly recognized the necessity of treating both mind and body as a single unit" (Page 4) and "Psychosomatic medicine is not a new science." (Page 9).

On the whole this book is praiseworthy and, indeed, instructive. There should be more thought given to mental hygiene, some dogmatic statements are unhealthy, such as that on Page 71, "With a disease as important and as uniformly fatal as hypertension, it is natural that the problem of treatment should have been attacked from many angles." Is hypertension uniformly fatal? Perhaps the discussion of "high blood pressure" has done more harm than the disease.

This book should stimulate interest in medical progress which is surely a worthy cause.

## NOTICES

### ANNOUNCEMENTS

Drs. Henry J. Bakst and Harold L. Chandler announce their association for the practice of internal medicine at 48 Beacon Street, Boston.

Dr. Nathan Crosby Norcross announces the removal of his office to Medical Arts Center, 354 Hobart Street, Oakland, California, for the practice of neurological surgery.

Dr. Volta R. Hall announces the removal of his office to 422 Beacon Street, Boston.

Dr. Leon Ryack announces the removal of his office to 1093 Beacon Street, Brookline.

(Notices concluded on page xvii)

## NOTICES (Concluded from page 890)

## RESIDENCY IN RADIOLOGY

Applications will be considered for appointment for a residency in radiology at the Joseph H. Pratt Diagnostic Hospital and Boston Dispensary from physicians with one or two years training in radiology. There are about 24,000 diagnostic examinations yearly (medicine and pediatrics). There are also active services in the tumor clinic and therapy department and many teaching conferences. Appointments will be made for one year. Applications should be addressed to Mr. Richard T. Viguiera, Administrator, Joseph H. Pratt Diagnostic Hospital, 30 Bennett Street, Boston 11.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY JUNE 24

## FRIDAY JUNE 25

\* 10-10:00 a.m. The Treatment of Migraine. Dr. John R. Graham. Joseph H. Pratt Diagnostic Hospital.  
\* 10:00 a.m. 12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

## TUESDAY JUNE 29

\* 1-15 1:15 p.m. Clinicooncogenetological Conference. Peter Bent Brigham Hospital.  
\* 1:30 2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

## WEDNESDAY JUNE 30

\* 10-10:00 a.m. Experimental Studies on the Restoration of the Circulation. Dr. Allan D. Callow. Joseph H. Pratt Diagnostic Hospital.  
\* 12:00 m.-1:00 p.m. Clinical Conference. (Children's Hospital) Ambulacator. Peter Bent Brigham Hospital.

\* Open to the medical profession.

June 17-20. American College of Chest Physicians. Page 455. Issue of March 25.

June 18-21. American Association of Medical Milk Commissioners Inc. Page 470. Issue of June 3.

June 20. American College of Radiology. Page 722. Issue of May 13.

June 20. National Conference of County Medical Society Officers. Page 734. Issue of May 20.

June 20 and 21. American Radiology Society. Page 543. Issue of April 8.

June 21 and 22. American Society for the Study of Sterility. Page 354. Issue of March 11.

June 23. Tufts Medical Alumni Association. Page 856. Issue of June 10.

June 23. University of Pennsylvania Medical Alumni Society. Page 678. Issue of May 6.

June 25 and 26. Christian Medical Society. Page 492. Issue of April 1.

June 28-30. American Academy of Pediatrics. Hotel Schroeder, Milwaukee, Wisconsin.

June 28-July 23. Harvard Seminar on Health Education. Page 856. Issue of June 10.

July 5-24. Students International Clinical Congress. Page 455. Issue of March 25.

July 12-17. First International Polymyositis Conference. Page 36. Issue of January 1.

August 11-21. International Congress on Mental Health. Page 344. Issue of March 4.

August 23-26. International Society of Hematology. Page 419. Issue of March 18.

August 26-28. American Association of Blood Banks. Page 470. Issue of March 18.

September 7-11. American Congress of Physical Medicine. Page 582. Issue of April 15.

September 13-15. American Academy of Pediatrics. Olympic Hotel 1, Seattle, Washington.

September 16-18. Vermont State Medical Society Annual Meeting, Burlington.

September 20-23. American Hospital Association. Page 310. Issue of February 26.

September 29. Mississippi Valley Medical Editors Association. Page 170. Issue of January 29.

October 6-9. American Board of Ophthalmology. Page 170. Issue of January 29.

November 1-3. American Clinical and Climatological Association. Page 582. Issue of April 15.

November 8-12. American Public Health Association. Page 420. Issue of March 18.

November 10-13. Association of Military Surgeons of the United States. Page 722. Issue of May 13.

November 20-23. American Academy of Pediatrics. Annual Meeting, Atlantic Hotel, New Jersey.

December 7-9. Southern Surgical Association Annual Meeting. Page 343. Issue of April 8.

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Number 26

## FOCAL EPILEPSY\*

### A Statistical Study of Its Causes and the Results of Surgical Treatment

#### I Epilepsy Secondary to Intracranial Tumors

JAMES C. WHITE, M.D.,† CHING TUNG LIU, M.D.,‡ AND WILLIAM JASON MIXTER, M.D.§

BOSTON

THE neurologists and neurosurgeons of the Massachusetts General Hospital have long been interested in determining the causes of epileptic seizures in patients both acutely and chronically affected. Therefore, all epileptic patients admitted to the wards have been studied with special care for evidence of focal compression or scarring of the brain. Air studies by either pneumoencephalography or ventriculography, have been performed routinely in these patients, and electroencephalography since 1937. We have selected the decade 1935-1944 for statistical review because it gives a period extending from twelve to a minimum of two years for the evaluation of surgical results. These patients with seizures amenable to surgical treatment fall into two broad groups, depending on whether the epileptogenic discharge arises from the irritating action of an expanding lesion or a cortical scar.

#### MATERIAL

Of 1130 patients admitted to the Massachusetts General Hospital with all varieties of epilepsy in the 1935-1944 decade, 240 have had seizures<sup>¶</sup> arising from an area that could be localized by clinical signs, pneumography and electroencephalography. In all these cases the disease has been verified by exploratory craniotomy, the patients in whom a definite lesion could be found therefore comprise 21 per cent of the total admissions for epilepsy. For descriptive purposes we have divided this series into two groups: 160 cases of cerebral compression

caused by intracranial tumors and 80 cases of acute or chronic epilepsy due to trauma or infection. The first part of this paper concerns the relation of tumors of the brain to epilepsy, with a review of the cases on which we have satisfactory information. The results in a small number of other patients operated upon in this hospital, but not observed by any of us, are omitted from this statistical analysis. In a succeeding article, we shall discuss the production of convulsions secondary to intracranial injury or infection and the results of surgical intervention in this group.

When seizures are associated with an expanding tumor of the brain the convulsive state is usually set off by local irritation in the zone of compressed ischemic cortex. In the infiltrative tumors, particularly the glioblastoma multiforme, there is in addition more or less vascular thrombosis, which produces further necrosis of the cerebral gray and white matter in advance of the actual tumor. The source of the epileptic discharge is always found in the peripheral area of damaged brain—never in the electrically inert expanding tumor itself.

The 160 tumors giving rise to convulsive attacks may be subdivided according to their location above or below the tentorium, their compression of the brain from without or invasion from within and, to a lesser extent their proximity to the motor cortex. The relation of the position of the tumor to the incidence of complicating seizures is demonstrated in Table 1. The incidence of seizures is highest in tumors close to the motor sensory areas of the cerebral cortex, and the chances of epilepsy are about the same regardless of whether the tumor compresses the cortex from without or invades it from within. These findings corroborate the statements of Penfield, Erickson and Tarlov.<sup>1</sup>

The most striking feature of our statistics is the frequency of epileptic seizures in patients with brain tumor. Epilepsy occurred in 25% of

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†Assistant professor of surgery, Harvard Medical School; chief, Neurosurgical Service, Massachusetts General Hospital.

‡Resident in neurosurgery, Graduate Hospital of the University of Pennsylvania; formerly research fellow in neurosurgery, Massachusetts General Hospital.

§Member, Board of Consultation, Massachusetts General Hospital.

¶Although the type of epilepsy observed in the great majority of these patients was the classic Jacksonian focal seizure, some had generalized attacks and others only hallowatory auras. The petit mal form of epilepsy, however, rarely if ever starts from a superficial focus and is therefore not amenable to surgery.

641 patients with intracranial tumors operated upon during this period. In tumors of the cerebral hemispheres the incidence of seizures is as high as 34 per cent. This figure is lower than that given by Penfield and Erickson,<sup>2</sup> who record an over-all incidence of convulsive seizures in 37 per cent of all intracranial tumors and 45 per cent in the supratentorial cases. However, as the authors point out, others have reported an incidence of convulsions considerably closer to our figures. Thus, Sargent<sup>3</sup> gave a figure of 30 per cent after exclusion of pituitary and cerebellar tumors, Dowman and Smith<sup>4</sup> one of 39 per cent with some form of epileptiform seizure, Parker<sup>5</sup> 21.6 per cent of focal seizures, Fur-

order of the type of their attacks) leads to the following conclusions:

One patient (M T), with an acoustic neuroma, suffered from typical ictus subtentorialis as described by Penfield and Erickson.<sup>2</sup> She had syncopal attacks in which she became dizzy and collapsed, losing consciousness for a few minutes. At these times she often "became stiff all over" (tonic postural seizures). After subtotal removal of the tumor she remained free of seizures for three years.

Another patient (S S) suffered from episodes of vertigo with staggering to the left followed by

TABLE 1 *Relation of Location of Tumor to Incidence of Seizures*

LOCATION	TOTAL NO OF CASES	CASES WITH EPILEPSY	INCIDENCE OF EPILEPSY	INCIDENCE IN PENFIELD'S SERIES
			%	%
Frontal	126	42	33	53
Parietal	76	35	46	68
Temporal	64	25	39	48
Frontoparietal	46	18	39	71
Occipital	14	2	14	32
Parieto-occipital	23	3	13	47
Temporo-occipitoparietal	9	4	44	40
Frontotemporal	12	3	25	80
Parietotemporal	38	9	23	67
Frontoparietotemporal	11	3	27	—
Temporo-occipital	3	0	0	—
Suprasellar and sellar (including pituitary)	53	4	8	8
Pineal	7	1	14	—
Third ventricle	8	1	12	32
Thalamic and basal	10	2	20	8
Infratentorial	125	7	5	3
Miscellaneous (lateral ventricles, corpus callosum, optic tract, exact extent of tumor not known and so forth)	16	—	6	—
Totals	641	160		
Averages			24.9	37

low and Sachs<sup>6</sup> 31.4 per cent among 248 verified intracranial lesions, and Pedersen<sup>7</sup> 29 per cent of 586 verified tumors.

Our finding of 7 cases of epilepsy among 125 infratentorial neoplasms is in fairly close agreement with the 3 per cent incidence reported by Penfield and Erickson<sup>2</sup> from the Montreal Neurological Institute. These writers have stated categorically that true epilepsy cannot result from a lesion limited to the posterior fossa, but that tumors compressing the lower brain stem and cerebellum may lead to what they have termed "ictus subtentorialis." Episodes of this sort consist of irritative stimulation of the lower cranial nerves, transient vertigo and syncope, in addition to tonic postural seizures with extensor rigidity and opisthotonos. On the other hand, Hoefer et al.,<sup>8</sup> in a review of a series of brain tumors at the New York Neurological Institute, have described 5 cases of posterior-fossa neoplasms that they considered to be the cause of true epileptiform attacks.

A review of the seizures that occurred in our 7 patients (not in chronological sequence, but in

several syncopal attacks, during which his parents observed no convulsive movements. At operation this nineteen-year-old boy was found to have a large medulloblastoma. After intensive radiation he began to have generalized seizures in his sleep, but on medication these have ceased during the past sixteen months. As Penfield and Erickson<sup>2</sup> have pointed out, a tumor of this type may metastasize via the subarachnoid space and give rise to true epilepsy by the development of a cortical focus.

A third patient (E S), with a large acoustic neuroma, suffered from intense vertigo and periods of syncope. A single generalized convulsive seizure was witnessed a month after operation.

In another case of acoustic neuroma the seizures developed only after operation and discharge from the hospital. As no accurate description of these spells could be obtained through the Social Service Department, it is impossible to draw any conclusions from this case.

The fifth patient (D B) had attacks of cerebellar vertigo. In addition there were seizures in

which the right arm was thrust out but did not shake, accompanied by transient loss of consciousness. This patient was an athletic young woman who also gave a history of several head injuries incurred while she was riding and diving, it is therefore conceivable that she had a traumatic focus in the cerebral cortex as well. At operation a midline necrotic tumor was biopsied that had the gross appearance of a medulloblastoma but on histologic examination could not be classified.

A child of two years (J D) developed attacks of syncope and rigidity in addition to several generalized seizures. These episodes of syncope were indistinguishable from certain forms of petit mal, which occur in persons without any suggestion of infratentorial lesion, and were accompanied by brain waves with the wave-spike contour. Evaluation of the origin of these seizures was further complicated by the fact that this child also suffered from hypoglycemia, with a blood sugar on several occasions below 50 mg per 100 cc. At operation a midline cystic astrocytoma was found, with separation of the cerebellar hemispheres.

In the last patient (A L) a hemangioma of the choroid plexus was partially removed from the fourth ventricle and may well have extended up the ventricular system above the tentorium. He had major seizures, with tonic stiffening of the left leg.

Electroencephalograms were done on only 4 of these 7 patients. The other 3 were cared for before the advent of routine testing. The brain waves were of the fast normal type in the patient with unequivocal ictus subtonialis of the syncopal and tonic postural types (M T). The presence of wave-spike activity has already been mentioned in the child who may have had true ictus subtonialis (J D). The electroencephalogram in the second patient (S S) was abnormal and indicated diffuse, widely scattered slow activity. Seizures in the fourth patient did not begin until after operation and discharge. The preoperative electroencephalogram showed diffuse moderate slowing.

Hoefer, Schlesinger and Pennes,<sup>3</sup> who have recently gone over the statistics from the New York Neurological Institute, give an over-all incidence of 30 per cent of epilepsy in their series of 595 cases of brain tumor. Excluding their infratentorial and midline lesions, a third of the tumors invading the hemispheres led to epilepsy. The greater incidence of seizures in the Montreal series may be explained by Dr. Penfield's well known interest in epilepsy. Considering all the above figures, it seems fair to say that seizures occur in nearly a third of all intracranial tumors.

Our experience, therefore, corroborates the statements of Penfield and Erickson,<sup>4</sup> who believe that

no typical epileptic seizure can result from a lesion limited to the cerebellar cortex or brain stem. These authorities cite the fact that it is impossible to induce convulsive seizures by electrical stimulation of these structures. Of their 4 cases of infratentorial tumor with major seizures of the type generally

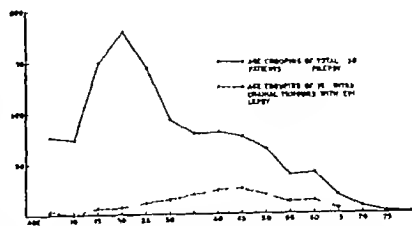


FIGURE 1 Relation of Age to Incidence of Epilepsy

recognized as cerebral in origin, 2 were due to medulloblastoma with metastatic lesions in the cerebral hemispheres. In another case the seizures were explained by cortical compression from ad-

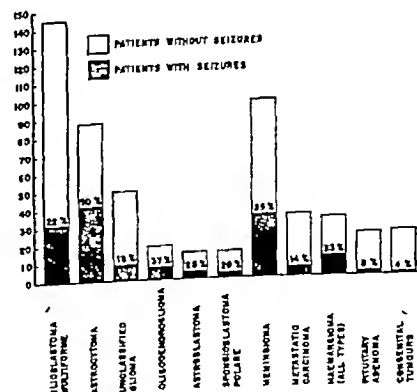


FIGURE 2 Incidence of Seizures among Patients with the Principal Supratentorial Tumors

vanced hydrocephalus, and in the fourth by concomitant idiopathic epilepsy. Ictus infratentorialis is therefore a warning signal of serious compression of the brain stem. These attacks involving the lower cranial nerves, often accompanied by transient vertigo and syncope, as well as tonic postural seizures with extensor rigidity and opisthotonos, are caused

by irritative stimulation of the medullary and adjacent structures

In our experience, as in that of Penfield and Erickson,<sup>2</sup> deeply situated tumors in the basal ganglia and third ventricle rarely gave rise to seizures (Table 1). We have encountered no case of "diencephalic epilepsy" similar to that described by Penfield.<sup>9</sup> Typical epilepsv is also rare in the

Since the great proportion of seizures due to birth injury or idiopathic epilepsy start in childhood or early adult life, it can be stated that *when epilepsy begins in adult life without a previous history of cranial trauma, cerebral abscess or encephalitis, the most probable diagnosis is tumor of the brain*

The type of lesion is a matter of further importance in the genesis of convulsions. The cytologic origin and the intracerebral or extracerebral situation of the common malignant and benign tumors located above the tentorium are shown in Figure 2, study of which reveals that the greatest incidence of epilepsy occurs in association with the astrocytic tumors of the glioma group and with the meningiomas. In the lesions that invade the hemisphere diffusely the lowest proportion is in the glioblastoma multiforme and metastatic carcinoma. As already pointed out by Penfield and Erickson,<sup>2</sup> the more slowly the tumor grows, the greater its epileptogenic tendency is likely to be.

#### RESULTS OF OPERATION

For the neurosurgeon who has to operate on these patients and also for the physician who refers the patient to him, the primary concern is to save or prolong life by radical resection. The fact that epileptiform seizures may continue, even after apparent total removal of a meningioma or cystic astrocytoma, is often lost sight of. So is the fact that, after resection, epilepsy may develop later when none existed before the operation. Because of the patient's gratitude that his life has been spared and because these seizures are often mild, this fact has seldom been emphasized. It is well, however, to realize this unpleasant possibility. Over-all statistics, which cover these points, are given in Table 2 and in the following paragraphs.

To express more clearly the effect of surgery on the epileptic complications of intracranial tumors, a brief summary of each of the more frequent varieties is included.

#### Astrocytoma

These gliomas may invade the brain diffusely or may remain partly encapsulated growths. The most favorable types are cystic and may contain only a small area of active tumor. These are generally limited to children and do not cause epilepsy because they characteristically occur in the cerebellum. Unfortunately, the epileptogenic astrocytomas of the hemisphere are most often the diffuse variety in which total extirpation is usually out of the question. In our series, as in that of Penfield and Erickson,<sup>2</sup> astrocytoma is the tumor that most frequently leads to epilepsy. In this ten-year period we have operated on 88 patients of this group, exactly half of whom had accompanying epilepsy. Sixty-nine of these astrocytomas lay above the tentorium, with a seizure rate of 62 per cent. In 3 out of 4 the onset of seizures had been the first

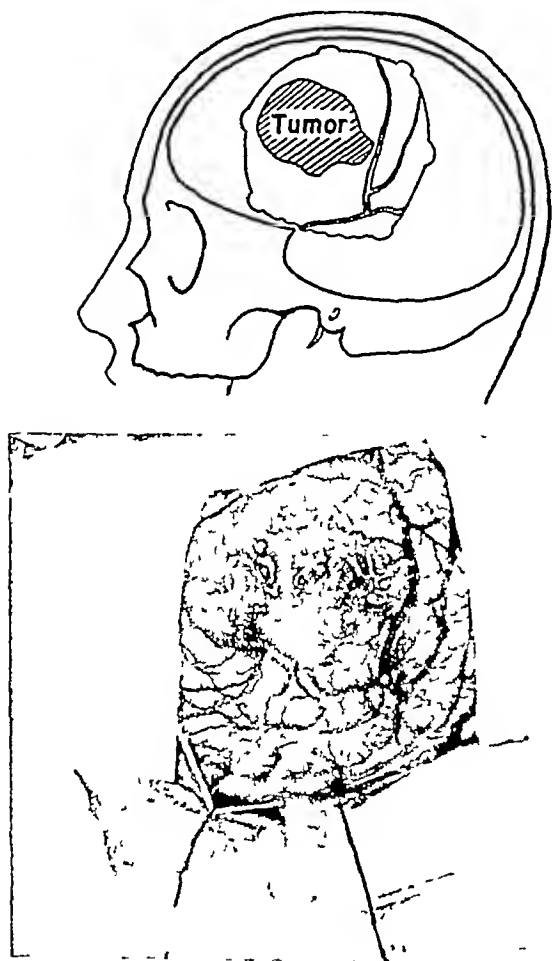


FIGURE 3 *Astrocytoma Presenting in the Left Frontoparietal Cortex*

*This forty-four-year-old woman gave a ten-year history of right-sided Jacksonian seizures. She had only recently developed mild aphasia and right hemiparesis. Partial resection of a deeply invasive tumor was done in 1939, after which there was improvement in speech and hemiparesis for two years, but seizures were only slightly reduced. She died four years after operation and fourteen years after the onset of epilepsy.*

pituitary adenomas, unless they have escaped from the sella and are expanding upward between the hemispheres or laterally into the temporal lobe (Jefferson<sup>10</sup> and White and Warren<sup>11</sup>).

Another important factor in the relation between tumor and epilepsy is the age of the patient, since the greater proportion of brain tumors in children invade the cerebellum and brain stem, where the tendency to produce seizures is at its lowest (Fig. 1).

suggestion of disease, often antedating any other evidence of the expanding intracranial mass by a period of months or even years. The following case report is of interest in this connection, especially as it refutes the commonly accepted rule that a normal pneumogram precludes the presence of a brain tumor.

A 40-year-old traveling salesman suffered his first seizure after becoming intoxicated at a business banquet in Boston. He was examined by Dr. Stanley Cobb, who found no evi-

as the first sign of disease in 75 per cent. Figure 4 illustrates a typical tumor of this sort. Both the glioblastoma and the astrocytoma diffusum invade the brain so extensively that there is seldom any chance of total resection and cure. Whereas extensive, although partial, removal of the larger astrocytomas may lead to considerable improvement of epilepsy, the results in this most malignant type of glioma have been all but worthless, only 1 out of 19 patients showing any improvement. Epilepsy not

TABLE 2 Results of Operation in Cases of Tumor with Epilepsy

Tumor	Cure* of Epilepsy	Great Improvement	Slight Improvement	No Improvement	Post-operative Convulsions Only	Death, or Inadequate Post-operative Follow-up	Cases with Epilepsy	Total No. of Tumors in Ten Yr.	Incidence of Epilepsy %
Glioblastoma multiforme	—	—	1	17	1	13	12	145	22
Astrocytoma	—	6	—	22	3	11	44	88	50
Unclassified glioma	—	2	2	2	1	2	9	50	18
Oligodendroglioma	—	2	—	—	—	3	7	17	37
Astroblastoma	—	—	1	—	—	2	4	15	26
Ependymoblastoma polare	—	—	—	—	—	2	3	20	20
Medulloblastoma	—	—	1	—	—	—	—	26	4
Glioma of chiasm	—	1	—	—	1	—	1	2	100
Pneumoma	—	—	—	1	1	—	1	7	14
Meningioma	—	—	—	1	—	—	—	35	14
Metastatic carcinoma	3	9	3	4	5	9	35	99	35
Lesions of blood vessels	—	—	—	4	—	1	5	16	14
Pituitary adenoma	1	6	1	2	—	2	11	33	33
Acoustic neuroma	1	—	—	1	1	1	3	24	8
Cerebral hemangioma	—	—	—	—	—	—	—	42	7
Others	—	—	—	—	—	1	1	22	4
Totals	—	—	—	—	—	—	—	16	0
Average	7	26	10	58	12	48	160	641	24.9

\*Patients listed as "cured" had no seizures after discharge from the hospital. Those listed as "greatly improved" had only very rare spells, and rarely long periods with complete freedom from attacks; they considered their results excellent and were all able to lead relatively normal lives.

†This group includes the craniofibrogliomas, epidermoids and dermoids.

dence of increased intracranial pressure and no abnormal neurologic signs. A pneumoencephalogram revealed no deformity in the well filled ventricles or subarachnoid space. A year later at a similar business convention in Minnesota the patient suffered a second series of seizures. Pneumography repeated at the Mayo Clinic showed a definite filling defect, and Dr. W. McK. Craig was able to remove a large amount of astrocytoma from the left frontoparietal area.

In our 33 patients who were operated upon and adequately followed, the incidence and severity of seizures have been reduced in 8, so that 6 have been able to return to work, 22 have been unimproved. Not one has been completely freed of seizures. Epilepsy, not present before operation, has developed subsequently in 3 cases. The reason for these poor results, so far as the seizures are concerned, is inherent in the invasive character of many of the tumors and the tendency for those which most frequently give rise to seizures to involve vital areas of the brain. A typical tumor of this type (Fig. 3) shows the difficulties of relieving these patients of their seizures, although the duration of life may be greatly prolonged.

#### Glioblastoma Multiforme

In 145 glioblastomas encountered in this decade, 32 (22 per cent) were productive of seizures. In cases in which seizures were present they occurred

present before operation developed subsequently in only 1 case.

#### Oligodendroglioma

We have encountered only 19 examples of this glioma, which in its rate of growth is situated midway between the astrocytoma and the glioblastoma. Seven gave rise to seizures (37 per cent). Only 4 of these are suitable for evaluation, with much improvement in 2, and no reduction of the seizures in the others.

Among the other varieties of glomatous tumors our material is too limited to draw any definite conclusions, but the figures are included in Table 2.

#### Meningioma

It is not surprising that this slowly growing tumor, which arises from the meninges and causes local compression of the brain, should be a frequent cause of convulsive manifestations. This was true in 35 of our 99 cases. In these, seizures were the primary symptom in 47 per cent. In the series from the Montreal Neurological Institute 67 per cent of the growths were associated with epilepsy, and this incidence was almost the same as that with astrocytoma. In the New York series of Hoefel et al. 46 per cent of the patients with astrocytomas



suffered from seizures, as against 37 per cent of those with meningiomas. Our series is comparable to the latter, 35 per cent being productive of seizures, as against 50 per cent of the astrocytomas. Unfortunately, Cushing and Eisenhardt<sup>12</sup> gave no over-all

result because the patient had a few minor seizures two years after the operation when she got overtired. There have been no further attacks, the area of decompression remains soft, and she is able to lead a perfectly normal life.

In the 26 cases with seizures in which adequate follow-up observations are available, 5 patients have had complete relief, 9 great improvement, and 3 only slight benefit, whereas in 4 the convulsive state has continued, even though removal appeared complete in all but 1. Five others developed their first seizures after what appeared to be successful extirpations. All these postoperative seizures were successfully controlled with medication. In the series reported by Groff<sup>13</sup> from the University of

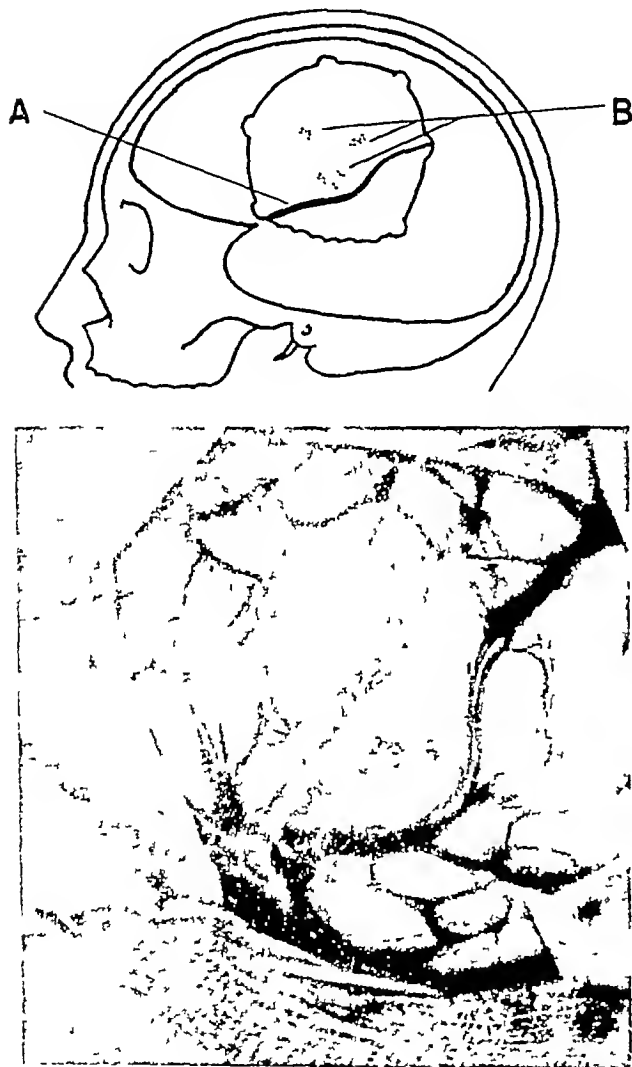


FIGURE 4 Left Temporoparietal Glioblastoma Multiforme in a Forty-Eight-Year-Old Man with a One-Month History of Aphasia, Right Hemiparesis and Jacksonian Seizures, Which Began in His Arm.

Operation resulted in no improvement, and the patient died four months later.

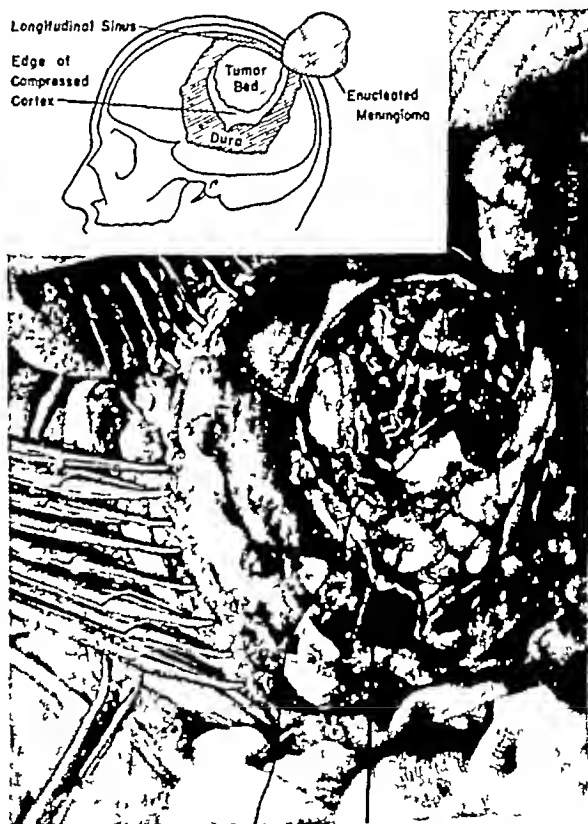


FIGURE 5 Left Parasagittal Meningioma in a Forty-Three-Year-Old Woman with a History of Intermittent Episodes of Paresthesia in the Right Arm for Four Years, Followed by Jacksonian Seizures of Two Years' Duration.

She described these attacks as beginning with a cold, numb feeling in the right arm and hand, followed by acute pain with tonic flexion of the fingers. This sensory aura spread down the right side. As the foot became involved the patient lost consciousness and had a typical major seizure. After removal of the tumor in 1939 the patient has remained well and free of seizures to date.

figures for the incidence of epilepsy in their great series of meningiomas, although they commented on the fact that the continuance of seizures after removal of the tumor was often "highly disconcerting."

Figure 5 illustrates a large parasagittal meningioma, which produced severe compression of the sensory-motor cortex with frequent epileptic seizures. Total extirpation of the growth, as shown in this photograph, has resulted in a seven-year period of improvement. This case is not listed as a perfect

Pennsylvania and also those by Penfield, Erickson and Tarlov<sup>1</sup> the incidence of seizures postoperatively was quite similar. In explanation of the continued attacks and the postoperative onset of seizures Penfield et al. state

Even an encapsulated meningeal fibroblastoma removed with meticulous care, usually leaves behind it, in the area of maximum impingement on the brain injury or absence of pia mater. This results in scar and continuing abnormality of cortical circulation.

### Metastatic Carcinoma

Only 5 out of 35 patients with carcinomatous metastases had accompanying seizures. In 4 cases, in which the lesion appeared to be well demarcated and was thought to have been "totally" excised, no lasting improvement followed. These patients may well have had other metastases, or the lesion may have rapidly recurred. Figure 6 illustrates this condition in a forty-three-year-old woman with primary bronchogenic carcinoma. The seizures always began with a sensation of tingling in the fingers of the left hand, and the electroencephalogram showed a small localized focus of cortical dysfunction in the midline just posterior to the junction of the coronal with the sagittal suture. Intracranial pressure was not elevated, and the pneumoencephalogram showed only a minimal deformity of the right lateral ventricle. In a later ventriculogram there was an added suggestive filling defect at the tip of the right ventricle, so that the patient may well have had a second metastatic tumor. The mass infiltrating the sensory cortex (Fig. 6) was excised with a wide margin. Although she never had any further seizures, she was reported to be having signs of recurrence within the brief period of two months, and she died four months after operation.

### Pituitary Adenoma

In our series of 24 pituitary tumors only 2 patients have exhibited epilepsy. One of these was seen in a Navy hospital, and this case has been reported because of the unusual size of the tumor.<sup>11</sup> In these 2 patients with seizures, as emphasized by Jefferson,<sup>10</sup> the chromophobe adenomas had expanded far beyond the usual confines of these lesions. The smaller had grown directly upward and was compressing the chiasm and floor of the third ventricle from below. Subtotal resection resulted in only slight temporary improvement, and the patient died of a recurrence three years later. In the other patient, who entered the hospital in status epilepticus, the tumor was so extensive that only a relatively small portion could be removed. At post-mortem examination this patient was found to have a chromophobe adenoma weighing 150 gm. and extending backward beneath the brain from the tip of the anterior fossa to the mid-pons. When epilepsy is seen in conjunction with an adenoma of the pituitary body, it is a danger signal indicating that the tumor is expanding widely beyond the sella turcica.

### Tumors of Blood Vessels

Thirty-three tumors of the cerebral blood vessels are listed in Table 2, of which 11 gave rise to seizures.

Histologically they fall into two groups, the deep hemangiomas composed of small vessels and the larger caliber angiomas or racemose aneurysms. The capillary hemangiomas, especially the cystic type seen in Lindau's disease, usually occur in the cerebellum and are therefore not a common cause of seizures. We have encountered 11 cases of noncystic

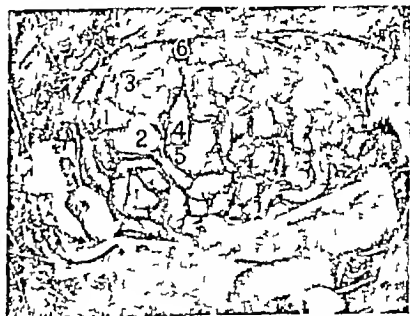
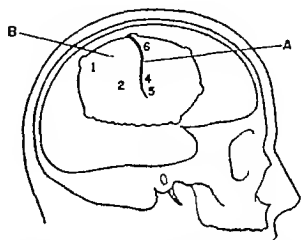


FIGURE 6. Carcinoma of the Bronchus with Metastasis to the Right Parietal Cortex.

A history of weakness of the left arm of four months' duration was presented. Jacksonian seizures began with an aura of tingling in the fourth and fifth fingers of the left hand. Operation in 1938 with electrical stimulation of cortex and resection of a small superficial metastatic tumor. Seizures ceased after operation but the patient progressively failed, dying in four months.

A = Rolandic vein and B = Carcinomatous infiltration of pia (see marker No. 3 in photograph). 3—alt. 60-cycle stimulus at marker No. 1 caused tingling in the little and ring fingers; at No. 2, tingling in the thumb and index finger; at No. 4 contraction of the hand and index finger; at No. 5 contraction of the orbicularis oculi and at No. 6 contraction of the hip.

cavernous hemangiomas in the cerebral hemispheres, 6 of which gave rise to seizures. These were explored and extensive resections carried out in 2 patients, both of whom improved so that, despite very minor seizures, one was able to return to school and the other has been working full time as a lawyer for ten years. Of 2 others in whom only biopsy was performed followed by radiation one was greatly improved at five years, and the other not benefited.

One patient died after exposure of the tumor in the fourth ventricle. In the remaining case the tumor was not found at operation, but when post-mortem examination was performed eight months later a deep frontoparietal hemangioma was disclosed.

The superficial angiomas producing arteriovenous cirroid aneurysms of the cortical blood vessels (Fig

periods of five to six years in 2 others, whereas the fourth derived only slight benefit. In the fifth case, a baby, the mass of dilated vessels in the temporal lobe was decompressed, but the period of postoperative observation was too short for evaluation of the effect.

#### SUMMARY

It is apparent from this review that epilepsy is a very common complication of brain tumors, accompanying approximately 1 out of every 3 such growths when the hemispheres are compressed or invaded. When a middle-aged patient complains of epilepsy of recent onset, occurring without previous history of trauma or infection, tumor of the brain is the most probable diagnosis. The victim of this disease is actually fortunate if it begins in this fashion, for statistical evidence indicates that the tumor with accompanying early seizures is most likely to be growing slowly and situated near the surface of the hemisphere, either a meningioma or astrocytoma or an oligodendroglioma. If attention is paid to this important sign, an early search can be made for the lesion, and radical excision attempted before the patient has reached the critical advanced stage of the disease. Chances of "curing" the convulsive state, however, are not very good. Of the most common examples, 17 out of 26 patients with meningiomas have been improved, and 5 of these apparently cured of their seizures. Four failed to derive any benefit from total removal of the tumor, and 5 developed the first seizures after an apparently successful resection. In 33 cases of astrocytoma no patient has had an apparent cure, and in only 8 have the frequency and severity of the seizures been significantly reduced. Epileptic convulsions have continued in the remaining 22, owing to the surgical difficulty of totally eradicating the diffusely invasive forms of astrocytoma or avoiding the irritative action of the contracting scar after radical removal of these tumors. Three others suffered their first convulsions after operation. In 2 out of 4 patients with oligodendrogliomas, 1 has been entirely relieved of his seizures and the other greatly improved. In the more malignant glioblastoma multiforme and metastatic carcinoma of the brain we have no right to claim any definite benefit of more than a few months' duration. Epilepsy associated with other forms of intracranial tumors occurred in too few patients to permit deductions of any significance.

Lesions of the basal ganglions and third ventricle are infrequently a cause of epilepsy. When this complication is associated with pituitary adenomas it is a nearly certain sign that the tumor has expanded widely out of its usual site.

In our experience tumors that are definitely limited to the posterior fossa and have no other complicating factor usually produce atypical seizures associated with transitory attacks of vertigo, syncope and irritation of the lower cranial nerves. This

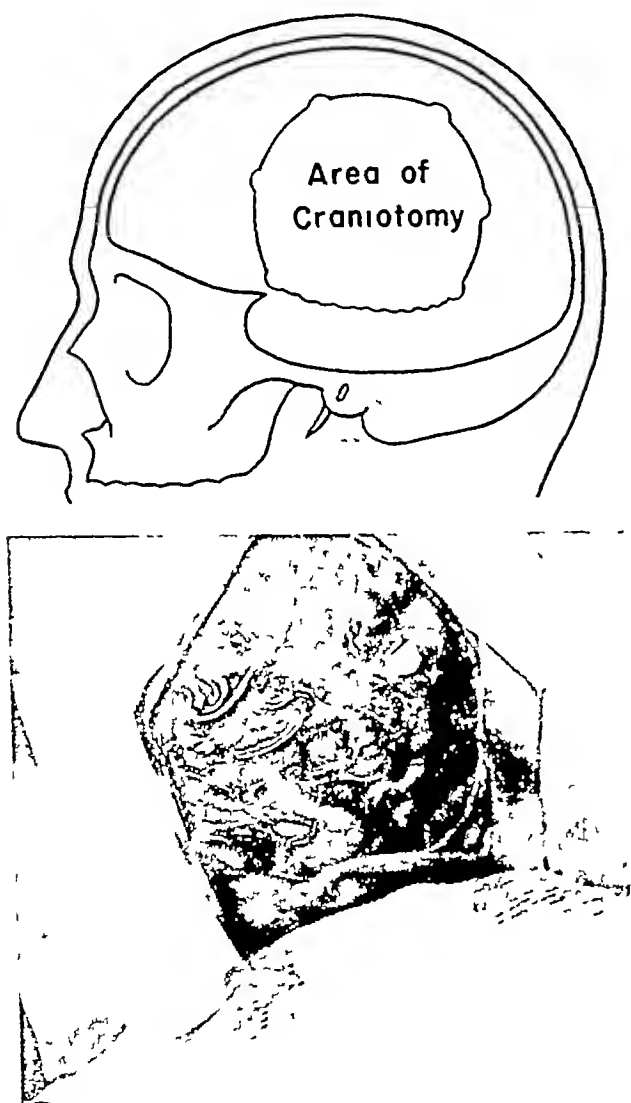


FIGURE 7 Angioma or Cirroid Aneurysm of the Left Parietal Cortex in a Thirty-Three-Year-Old Man Who had Noticed Numbness and Stiffness of the Right Arm and Hand for One Year, Followed Shortly by Jacksonian Seizures

Exploratory craniotomy in 1940 was followed by radiation therapy. Seizures improved, but recurred with heavy drinking, which necessitated commitment to an institution. Epilepsy was then controlled with anticonvulsant drugs, but he died four years later of tuberculosis with massive pulmonary hemorrhage.

7) are generally inoperable because of their extreme vascularity and the damage to the circulation of the brain that would result if extirpation were attempted. Radiation, however, which followed exploratory craniotomy in 4 cases, resulted in a five-year cessation of seizures in 1 and great improvement for

syndrome, classified as "ictus subtentorialis," is caused by compression of the pons or medulla. In the rare case in which typical major seizures occur, it is usually found that a medulloblastoma has implanted itself above the tentorium or that there is some other explanation.

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## SWIMMING POOLS\*

### Their Relation to Illness

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DURING the seven years 1941 to 1947 reasonably accurate records of swimming-pool attendance and of the incidence of respiratory-tract and communicable diseases have been kept at a boys' boarding school in Massachusetts for the purpose of determining whether a difference in frequency of these illnesses existed between those who used and those who did not use the swimming pool. Only boarding students have been considered in these records because of the difficulty of accurately determining the nature of all day students' illnesses. At this institution the season for competitive swimming and swimming-team training extends from the middle of November through the first week of March, but because of the changes in team personnel that occur during the early part of the season and because of the difficulty of assessing the duration of illnesses occurring prior to the Christmas holidays, this study covers only the winter term portion of the swimming season (approximately, the eight weeks subsequent to the first week of January). The interval studied is brief, but it is the period during which respiratory and communicable diseases are at their height, and any differences in incidence in these illnesses between boys who do and those who do not go into the pool should be accentuated at that time.

The swimming pool at this institution is equipped with a filtration and chlorination system. The chlorine level, reaction and bacterial content are determined frequently and have always been maintained at highly satisfactory standards. It has

been the policy immediately to close the pool for a short time should the chlorine level become either too high or too low or should any highly contagious and serious illness (such as a meningococcal infection) develop among the swimmers. It has also been the policy to exclude from the swimming group any boys whose past history indicates a marked susceptibility to infections of the middle ear or nasal sinuses<sup>1,2</sup>; this policy, however, has not been an ultraconservative one, and those who are alleged previously to have had frequent attacks of sinusitis but whose general condition is good are frequently permitted to elect this sport on a trial basis. No students except those regularly enrolled on the swimming squad are permitted to use the swimming pool during the winter term; this regulation is made not only to prevent overcrowding the pool but also to allow a better control of illness by confining the use of the pool to boys well known to the coaches. All swimmers are strongly advised against going into the pool when they have any symptoms of an upper-respiratory-tract infection, and the coaches have been alert and co-operative in enforcing this advice. To prevent malingering among and chiefly to maintain the condition of swimmers an exercise program called "dry swimming" is provided for all swimmers on days when minor-upper respiratory tract infections prohibit their going into the pool but do not contraindicate their having sufficient exercise to maintain their level of endurance and muscle tone. Such a supplementary exercise program is essential if one is properly to enforce a regulation that none with "colds" may swim, and

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at the same time both avoid malingering on this basis and prevent a deterioration in a swimmer's condition from lack of exercise. Strenuous exercise during the early stages of a severe common cold is not advocated, there is, however, a serious attempt to avoid the attitude that is rightly re-

ports of the incidence of respiratory-tract infections and the common communicable diseases over a period of the winter terms from 1941 to 1947 are presented below. There are also data concerning the number of admissions to the school hospital and the number of days spent in the hos-

TABLE 1 Number of Hospital Admissions\* among Regular Swimmers, Nonswimmers and Occasional Swimmers

YEAR	REGULAR SWIMMERS	NON-SWIMMERS	OCCASIONAL SWIMMERS	HOSPITAL ADMISSIONS PER REGULAR SWIMMER	HOSPITAL ADMISSIONS PER NON-SWIMMER	HOSPITAL ADMISSIONS PER OCCASIONAL SWIMMER
1941	96	488	80	0 770	0 690	0 770
1942	101	528	39	0 290	0 281	0 154
1943	80	523	37	0 389	0 222	0 108
1944	117	449	27	0 231	0 145	0 222
1945	150	470	37	0 140	0 191	0 270
1946	128	502	30	0 470	0 430	0 600
1947	143	540	17	0 189	0 174	0
Averages	117	500	38	0 354	0 305	0 303

\*Only admissions for diseases of the respiratory tract are considered

ferred to as the "abuse of rest." In my opinion athletes are "strained" or harmed by exercise only when they put forth strenuous exertion for which they have not been conditioned properly.<sup>4, 5</sup>

In this report three classes of students are considered: those who did not go into the swimming pool at all during the winter term (these are referred to as "nonswimmers," but this does not mean that they were unable to swim), those who went into the pool no more than seven times during the winter term (these are referred to as "occasional swimmers"), and those who elected swimming as their form of athletics for the winter term and whose attendance was regular except for such a

hospital. The main purpose has been to attempt to determine whether there is any significant difference in incidence of illness between boys who swim in an indoor chlorinated pool during a New England winter and those who do not do so. The category of "occasional swimmers" exists only because it did not seem proper to include students who went into the pool on the average only two or three times with those who swam regularly all term, and because it was obviously improper to classify them with the group made up of those who did not go into the pool at all. This discussion, for the most part, concerns a comparison of the "regular swimmers" and the "nonswimmers",

TABLE 2 Number of Cases of Respiratory Illnesses per Boy among Regular Swimmers and Nonswimmers

YEAR	COMMON COLD		INFLUENZA		ACUTE PHARYNGITIS		PRIMARY ATYPICAL PNEUMONIA		ACUTE BRONCHITIS		ACUTE SINUSITIS		OTITIS MEDIA		HEMOLYTIC STREPTOCOCCUS PHARYNGITIS	
	REGU-LAR SWIMMERS	NON-SWIMMERS	REGU-LAR SWIMMERS	NON-SWIMMERS	REGU-LAR SWIMMERS	NON-SWIMMERS	REGU-LAR SWIMMERS	NON-SWIMMERS	REGU-LAR SWIMMERS	NON-SWIMMERS	REGU-LAR SWIMMERS	NON-SWIMMERS	REGU-LAR SWIMMERS	NON-SWIMMERS	REGU-LAR SWIMMERS	NON-SWIMMERS
1941	0 610	0 460	0 100	0 160	0 040	0 040	0	0 004	0	0 002	0	0 002	0 010	0 008	0	0
1942	0 158	0 193	0	0 002	0 089	0 047	0	0 013	0 009	0 009	0	0 009	0 009	0 006	0 009	0 013
1943	0 200	0 092	0	0	0 125	0 073	0 013	0 015	0 025	0 015	0 013	0 008	0 013	0 015	0	0 007
1944	0 162	0 078	0	0 002	0 026	0 038	0 009	0 002	0 009	0	0 017	0 009	0 009	0 002	0 007	0 002
1945	0 093	0 108	0 007	0 023	0 027	0 017	0	0	0	0	0	0 004	0	0 007	0 007	0 010
1946	0 190	0 180	0 190	0 150	0 030	0 050	0	0 010	0	0 004	0 007	0 004	0 020	0 020	0 030	0
1947	0 119	0 146	0	0	0 049	0 020	0	0 002	0	0	0	0 002	0 007	0 002	0 007	0
Total cases	164	632	35	164	44	163	2	25	4	16	6	14	7	29	8	19
Average cases per boy*	0 190	0 170	0 140	0 150	0 050	0 040	0 002	0 007	0 005	0 004	0 007	0 004	0 008	0 008	0 009	0 005

\*For seven-year period except for influenza, average number of cases of which is given for 1941 and 1946 the only years in which it appeared in significant numbers

reason as illness (these are referred to as "regular swimmers"). The "occasional swimmers" consisted of those who preferred to change to some other sport early in the term or those who became ill early in the term and did not subsequently return to swimming.

the "occasional swimmers" because of their small numbers are referred to only in Table 1. The data in Table 1 indicate that over the winter terms of the seven years from 1941 to 1947 there was a slightly larger number of hospital admissions per boy on account of respiratory illness.

in the group of regular swimmers than in the other groups, except for one year (1945), when the incidence of this type of disease was at its lowest for the period studied. The average number of admissions for the seven years was about 14 per cent greater for the regular swimmers than for the others. The differences between these groups are slight, and it may be that illness was not even this much more frequent in the group of "regular swimmers"

such as influenza and hemolytic streptococcus pharyngitis would be expected to spread more widely among the swimmers, but they do not always do so. In 1941 the number of cases of influenza within the swimming group was 10 and that among the nonswimmers 78 (about 1.6 times as high a rate for the latter), but in 1946 there were 24 cases against 73, making the incidence 1.2 times higher in the swimming group. In 1945 the small total

TABLE 3 Number of Cases of Common Contagious Diseases per Boy among an Average of 117 Regular Swimmers and 500 Nonswimmers

YEAR	MEASLES		MUMPS		CHICKEN POX		SCARLET FEVER	
	REGULAR SWIMMERS	NON SWIMMERS	REGULAR SWIMMERS	NON SWIMMERS	REGULAR SWIMMERS	NON SWIMMERS	REGULAR SWIMMERS	NON SWIMMERS
1941	0 130	0 100	0 010	0 004	0	0	0	0 004
1942	0	0	0	0 004	0	0 017	0	0 004
1943	0 150	0 075	0 0 1	0 010	0	0 005	0	0
1944	0	0	0	0 002	0	0 015	0	0 000
1945	0	0	0	0	0	0	0	0
1946	0	0	0	0	0 007	0 002	0	0
1947	0	0	0	0	0	0	0	0
Total cases	24	87	1	10	1	22	0	4
Average cases per boy for 7-year period	0 029*	0 024*	0 000	0 003	0 0001	0 005	0	0 002

\*The averages on the basis of 1941 and 1943 alone are 0.100 for regular swimmers and 0.080 for nonswimmers.

but that the swimming coaches, being more conscious than other coaches of the effect of their sport upon respiratory disease, were more apt to send their boys to the school hospital. The variation in incidence of this type of illness from year to year (from 0.14 to 0.77 admissions per boy among the swimmers) indicates that conclusions are unre-

number of cases (12) makes the much higher incidence (over three times the frequency for swimmers) among the nonswimmers of little significance. During none of these winter terms was hemolytic streptococcus infection very prevalent—in 1946 5 of the 12 cases of pharyngitis from this source occurred in the swimming group, a frequency three

TABLE 4 Hospital Days per Boy on Account of Respiratory Illness during the Winter Terms of 1942-1947

YEAR	REGULAR SWIMMERS			NONSWIMMERS		
	NO OF PARTICIPANTS	TOTAL NO. OF INFIRMARY DAYS	NO OF INFIRMARY DAYS PER BOY	TOTAL NO OF PARTICIPANTS	TOTAL NO OF INFIRMARY DAYS	NO OF INFIRMARY DAYS PER BOY
1942	101	135	1.3	528	826	1.6
1943	80	175	2.2	521	676	1.3
1944	117	149	1.3	449	359	0.8
1945	150	87	0.6	470	333	0.7
1946	128	139	2.6	50	1161	2.3
1947	143	91	0.6	540	87	0.5
Totals	719	976	1.4	3012	3644	1.2

liable unless they are based on data collected over a period of several consecutive years.

The frequency of several of the respiratory tract illnesses is shown in Table 2. Common colds and acute pharyngitis were somewhat more prevalent (10 and 20 per cent respectively) among the swimmers than among the nonswimmers, and primary atypical pneumonia (of which there were only 27 cases within these two groups in seven years) occurred about three times as frequently among the nonswimmers. Diseases of high communicability,

times as great as that among the nonswimmers. There was no difference in the incidence of otitis media in the two groups for the entire period, but the rate for the small number of cases of acute sinusitis was almost twice as high among the swimmers.

There was not a large number of cases of the common contagious diseases in the student population during the seven-year period studied (Table 3). The number of scarlet-fever cases was small, and it is probably only due to chance and the small

number of cases that all these are found in the non-swimmers. Chance again probably explains the fact that although there were 9 cases of chicken pox in 1942 and 11 cases in 1944 among the non-swimmers, no cases appeared among the swimmers, since no initial case developed in a swimmer,

TABLE 5 *Number of Hospital Days per Boy for Each of the Winter Terms, 1941-1947\**

YEAR	HOSPITAL DAYS	
	REGULAR SWIMMERS	NON-SWIMMERS
1941	4 52	5 23
1942	1 59	2 42
1943	5 09	2 76
1944	1 50	1 40
1945	0 70	1 30
1946	2 80	2 61
1947	0 75	0 99
Averages	2 14	2 09

\*This table includes admissions for all types of disorders (respiratory, gastrointestinal, surgical, psychiatric and so forth)

there was no opportunity for contagion in the swimming-pool situation. The findings regarding mumps and measles, however, were quite different, and are of interest because of the fact that their viruses are found in mouth and nose washings. In 1941 there were 48 cases of measles among the non-

only the incidence of various respiratory illnesses within the swimming group but also the number of days spent in the hospital for these and other types of illness or injury. The sport may be more of a hazard to classroom attendance on the basis of a higher incidence of respiratory illness and the common contagious diseases but no more of a one from the standpoint of number of days lost because of these disorders. It is further possible that the days lost from *all* types of illness or injury may be no higher for the swimming group than for the nonswimmers; it is conceivable that the higher incidence of respiratory-tract and common contagious disease among the swimmers might be balanced by a higher incidence of other types of ailments in nonswimmers. Data giving the number of hospital days spent only because of respiratory-tract illness are presented in Table 4. The group that did not go into the swimming pool at all averaged, over this period of six winters, about 14 per cent fewer hospital days on account of respiratory illness than the group that swam regularly. In only two years was the number of hospital days lower for the swimmers than for the nonswimmers, but in the year 1946, in which the incidence of respiratory illness was the highest for this six-year period (Table 1), there were only slight differences

TABLE 6 *Hospital Admissions for Various Disorders, 1941-1947*

YEAR	ADMISSIONS FOR RESPIRATORY ILLNESSES		ADMISSIONS FOR COMMON CONTAGIOUS DISEASES		ADMISSIONS FOR MISCELLANEOUS AILMENTS	
	REGULAR SWIMMERS	NON-SWIMMERS	REGULAR SWIMMERS	NON-SWIMMERS	REGULAR SWIMMERS	NON-SWIMMERS
1941*	%	%	%	%	%	%
1942	82	63	15 5	15	2 5	22
1943	70	55	0	5	30 0	40
1944	49	47	27 0	18	24 0	35
1945	61	45	0	8	39 0	47
1946	70	60	0	2	30 0	38
1947	83	75	0	2	17 0	23
	90	63	3	3	7 0	34

\*In 1941 respiratory illnesses accounted for 82 per cent of hospital admissions among swimmers, and miscellaneous disorders and so forth for 2 5 per cent.

swimmers and a third more per boy among the swimmers. In 1943 there were 5 cases of mumps among the nonswimmers and six times as many per boy among the regular swimmers. When the number of cases is small, it is always difficult to determine the influence of chance, but these figures seem to be of some significance. In the presence of an initial case within a swimming group the possibility for the spread of measles and mumps seems to be much greater than that within a group not using a swimming pool.

One of the chief functions of a student health service is to keep students well and at their classes, the effect of any aspect of school life upon classroom attendance has to be considered and evaluated. Therefore, it is of interest to determine not

between the incidence and the hospital-day figures for these two groups.

It appears that other types of illness and injuries are a sufficient factor in the number of hospital days spent so that despite the higher incidence of respiratory illness among swimmers their average days spent in the hospital *from all causes* is only 2 per cent higher than that for the nonswimmers (Table 5). In four of the seven years the average number of hospital days was smaller for the swimmers than for the nonswimmers, and again the considerable year-to-year differences emphasize the need of extending such observations over a period of several years. The data in Table 6, showing the percentage of *all* admissions due to respiratory tract disease, suggest how this can be true, but

why there should be a lower percentage of admissions for other than respiratory or the common contagious diseases among the swimmers in each of the seven years is not clear. One factor may be the very low incidence of injuries at swimming as contrasted to other winter sports. In six consecutive years there was a total of four injuries at swimming,\* and in this period there were about ten times as many injuries per participant in such sport as wrestling and basketball as there were in swimming.

### SUMMARY

A comparison of the illnesses that developed among students at a boys' boarding school who used the swimming pool with those who did not do so indicates that in the seven-year period studied there was a higher incidence of respiratory illness among the swimmers. The number of hospital days spent because of respiratory-tract illness and the number of hospital admissions for the same cause were both about 14 per cent greater among the swimmers than among those who did not use the pool. There was, however, considerable yearly variation in both the incidence and the number of hospital days spent for this type of illness and it is clear that this does no more than reiterate the need for careful supervision of both pools and bathers so that excessive respiratory illness may be avoided. When careful control is exercised and

when normal conditions exist, there is on the basis of this experience, no reason to expect a high incidence of respiratory infection among swimmers. In the presence of a highly communicable disease, however, these data suggest that it is desirable to take extra precautions in this group. Mumps and measles seemed to spread more rapidly among the swimmers.

The number of hospital days spent for all causes was, over this seven-year period, practically the same for the swimmers as it was for those who did not go into the pool, the higher incidence of respiratory illness among the swimmers was balanced by a higher incidence of injuries and other ailments among the others.

In the presence of careful control and reasonable precautions it does not appear that the benefits of this swimming pool were overbalanced by its effect upon either the frequency or the duration of illness.

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## MYCOTIC ANEURYSM OF THE BRACHIAL ARTERY AFTER CURE OF BACTERIAL ENDOCARDITIS\*

### Successful Treatment by Surgical Excision

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THE occurrence of mycotic aneurysm secondary to bacterial endocarditis is comparatively rare. In 1923 Stengel and Wolferth<sup>1</sup> reviewed 217 cases, 187 of which had associated bacterial endocarditis. The sites of predilection were as follows: aorta, 66, superior mesenteric artery, 24, hepatic artery, 19, femoral artery, 16, splenic artery, 15, middle cerebral artery, 14, other intracranial arteries, 14 and brachial artery, 10. The authors pointed out that the most frequent sources of the primary infection, other than the heart, were located in the lung and in bone. Several attempts had been made to ligate

or to remove mycotic aneurysms but, according to these authors, "A considerable number of patients have died as a result of the operation or their death has apparently been hastened by it, and even those who recovered with a good local result usually died within a short time from their cardiac infection." This pessimistic attitude is no longer warranted in view of the high percentage of cures now obtained in the treatment of bacterial endocarditis with antibiotics. In a series of 44 patients treated with penicillin, Paul, Bland and White<sup>2</sup> reported cures in 29 (66 per cent). In 2 of the cases in which the treatment was a failure the patients died of ruptured mycotic intracranial aneurysms, and in 1 of these, cultures from the involved aortic valve and the heart's blood were sterile. It was postulated that the aneurysm, although sterile at the time of post-mortem examination, had developed as a result of previous weakening of the

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vessel wall by bacterial implantation before the blood stream had been effectively sterilized

Klein and Crowell<sup>2</sup> reported a cure with penicillin in a patient with endocarditis due to *Streptococcus viridans*. They successfully extirpated an aneurysm that had developed in the right ulnar artery just below the elbow.

The following is a report of another successful removal of a mycotic aneurysm that developed in the left brachial artery of a patient with endocarditis due to a Type VIII pneumococcus

### CASE REPORT

R L M, a 20-year-old, unemployed veteran of World War II, was admitted to the hospital on July 21, 1947, with the chief complaints of headache, stiff neck, chills and fever. He had had intermittent nasal obstruction and symptoms suggestive of sinusitis since a fracture of the nose in 1945. In April, 1947, a submucous resection was done. Physical examination at that time revealed no cardiac abnormalities. Because of the recurrence of sinusitis, the patient had quit his job in an asphalt plant about 1 month prior to admission. Nineteen days before admission he developed mild frontal headache and later, ill defined, migratory pains in the chest and abdomen. These symptoms continued in spite of treatment with nose drops and sulfadiazine. Two weeks before admission, he had chills, fever, nausea and vomiting, which also failed to respond to sulfadiazine therapy. On July 19, he was admitted to a hospital in another city, where he was found to have fever, a cardiac murmur and nuchal rigidity. He was transferred to this hospital.

Careful questioning of both the patient and his mother failed to elicit any past history suggestive of rheumatic fever or other serious childhood illnesses except for "pleurisy" at the age of 14, when he had been hospitalized for 1 week.

Physical examination disclosed a patient who was acutely ill and drowsy but well oriented and complaining only of headache and stiff neck. There was moderate nuchal rigidity, but there was no Kernig or Brudzinski sign. Periorbital edema was the only ocular abnormality. The pharynx and nasal mucosa were injected, and there was a moderate amount of mucopurulent post-nasal discharge. The lungs were normal to percussion and auscultation. Auscultation of the heart revealed a loud, rough, apical systolic murmur poorly transmitted to the left axilla and no diastolic murmur. There was no cardiac enlargement. The spleen was easily felt just below the left costal margin. The left ankle was slightly tender, but there was no swelling or erythema. There was mild clubbing of the fingers and cyanosis of the nails. There were no petechiae or skin changes and no lymphadenopathy.

The temperature was 104.8°F by rectum, the pulse rate 110, and the respiratory rate 24. The blood pressure was 100/50.

Examination of the blood revealed a red-cell count of 4,350,000, with 14.0 gm of hemoglobin, and a white-cell count of 16,800, with 88 per cent neutrophils, 10 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was 14 mm in 1 hour (Wintrobe method). The urinary sediment contained 5 to 10 red cells and 2 to 4 white cells per high-power field; subsequent urinalyses were negative. Each of two blood cultures revealed the presence of a Type VIII pneumococcus, which was sensitive to 0.02 units of penicillin per cubic centimeter. A serologic test for syphilis was negative. Roentgenographic examination of the chest, paranasal sinuses and skull was negative, and an electrocardiogram was interpreted to be within normal limits.

Lumbar puncture revealed an initial spinal-fluid pressure equivalent to 260 mm of water. Approximately 15 cc of turbid fluid was removed, and 20,000 units of penicillin was instilled intrathecally. Examination of the spinal fluid disclosed 264 white cells per cubic millimeter, with 86 per cent neutrophils and 14 per cent lymphocytes, a sugar of 65 mg, a protein of 45 mg per 100 cc and a chloride of 671 mg per 100 cc. No organisms were found on direct smear or on culture. The patient was given 100,000 units of penicillin intramuscularly every 2 hours, and 24 hours later the temperature had dropped to 97.8°F, remaining within normal

limits except for elevations to 100°F on the 2nd and 3rd days of therapy. The headache and stiff neck subsided on the 2nd day, the patient's appetite improved, and by the 4th day he was completely asymptomatic and ambulant.

A second lumbar puncture on the day after admission again disclosed an initial spinal-fluid pressure equivalent to 260 mm of water. The cerebrospinal fluid contained 46 white cells per cubic millimeter, with 72 per cent neutrophils and 28 per cent lymphocytes. Penicillin, 20,000 units, was instilled intrathecally and on the 2nd hospital day the spinal fluid pressures were normal and the fluid clear.

Penicillin was discontinued on August 4 after a total of 10,470,000 units had been given. Five blood cultures taken during the period of treatment and five taken at daily intervals after cessation of penicillin therapy showed no growth. The apical systolic cardiac murmur became less harsh and at times assumed a high-pitched quality. The spleen was no longer palpable on the 23rd hospital day.

Because of his apparent recovery, the patient was allowed to go on leave on August 13. During the trip home he experienced vague, intermittent pains in the right lower abdomen, lasting 12 hours. On the morning of August 15 he felt a sudden, sharp pain in the left axilla, with increasing discomfort during the day. He was seen by his physician at home, the left upper extremity was placed in a sling, and he returned to this hospital on August 16.

The apical murmur had not changed, the spleen was not palpable, and the only new physical findings were confined to the left upper extremity. There was extreme tenderness in the left axilla, with swelling, marked induration and increased warmth in the region of the first portion of the brachial artery about 5 cm distal to the apex of the axilla. Pulsations were palpable proximal but not distal to that site, but the radial pulse was palpable, though markedly reduced on that side. The entire extremity, however, was warm, and there were no color changes. Mild edema was present in the forearm and hand. The blood pressure was unobtainable on that side.

The temperature was 99.6°F by mouth, the pulse 100, and the respirations 20.

Examination of the blood disclosed a white-cell count of 13,800, with 62 per cent neutrophils, 36 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was 44 mm in 1 hour (Wintrobe method). The urinary sediment contained 5 or 6 red cells and 4 or 5 white cells per high-power field, but subsequent urinalyses revealed a normal sediment. Four blood cultures were sterile.

The diagnosis of brachial-artery occlusion was made, and the patient was given an initial dose of 300 mg of dicumarol, 50 mg of heparin intravenously every 4 hours and 200 mg of papaverine every 2 hours. A left stellate ganglion block was followed by some increase in warmth of the extremity but no increase in the intensity of the radial pulse.

Dicumarol was continued in amounts that maintained the prothrombin time between 19 and 29 per cent. Oscillometric determinations revealed markedly reduced pulsations in the first portion of the brachial artery and only slight oscillations below that point. The induration and tenderness at the site of thrombosis subsided within 3 days, after which the patient was allowed out of bed. An electrocardiogram on August 17 again revealed a normal tracing, and radiographic examination of the heart, including a barium swallow, revealed no abnormalities.

On September 4 a fusiform enlargement was noted for the first time slightly above the previous site of occlusion, and the oscillometric readings over this area were increased. On the following day, the patient complained of transient numbness and coolness of the hand, but no color change or diminution of the peripheral pulses was detected. In the next 3 days there were several transitory episodes of numbness unrelieved by a stellate ganglion block. On September 9 examination revealed an increase in the size of the pulsating mass, which measured about 5.0 by 2.0 cm. Rolling the mass under the fingers produced mild distal tingling (Tinel's sign), which was referred to the flexor surface of the thumb and index finger of the left hand. There was definite weakness of all the muscles supplied by the median nerve, and patchy hypesthesia to light touch and paresthesia to pinprick over the median sensory area. The diagnosis of brachial-artery aneurysm, with compression of the median nerve, was made, and the patient prepared for operation. He was given 60 mg of vitamin K intramuscularly every 3 hours during the night

and a transfusion of 500 cc. of whole, fresh blood. Prior to operation the next morning, the prothrombin time was 61 per cent.

On September 10 an incision was made over the first portion of the brachial artery. The median nerve was found lying in a groove in the aneurysmal sac. The median and ulnar nerves were dissected from the sac. The aneurysm was approximately 4 cm. in diameter, moderately thin walled and noncompressible. The proximal artery was patent and was occluded with a bulldog arterial clamp for 20 minutes during which the hand remained warm. The artery was then ligated proximally and distally and the sac with its vasa comitantes was removed. The distal artery was narrower than normal and contained a thrombus.

Gross tissue examination revealed a specimen consisting of a 37-cm. segment of brachial artery and vein, together with a small amount of perivascular tissue. Beginning 0.8 cm. below the proximal resected end and extending for a distance of 1.5 cm., the artery was dilated to a diameter of 3.2 cm. The vessel wall proximal to the aneurysmal dilatation was elastic, of normal thickness and lined by yellow smooth glistening intima. A branch artery arose from this portion. A groove previously occupied by the median nerve ran longitudinally along one side of the aneurysm which was filled with friable red thrombus. Its wall was thin, devoid of intima and hemorrhagic. Distal to the aneurysm, the artery was filled with a firmly fixed gray red thrombus which protruded from the resected end.

Microscopical examination of a section taken from the distal segment showed the lumen to be almost completely filled with an organizing thrombus containing well preserved red and white cells. The intima was destroyed at its point of attachment. In other areas the internal elastic membrane was broken up or absent. Numerous lymphocytes and a few polymorphonuclear leukocytes were present in the media, especially around the vasa vasorum. A few red cells were scattered between the muscle fibers. The mural architecture was completely destroyed and replaced by chronic inflammatory tissue in which fibrous tissue and lymphocytes predominated. Also present were neutrophilic and eosinophilic polymorphonuclear leukocytes, numerous macrophages filled with hemosiderin granules, areas of hemorrhage and small foci of necrosis. Cultures from the aneurysm and from the thrombus were sterile. The pathological diagnosis was chronic mycotic aneurysm of the brachial artery, with organizing thrombus.

The patient made an uneventful recovery and was discharged on the 15th postoperative day. He was seen 8 weeks after operation, when his only complaint was slight weakness and numbness of the left hand. Physical examination revealed that the apical systolic murmur had decreased in intensity, that no early or late diastolic, basal or apical murmurs had developed and that the median nerve function had improved. The left radial pulse was still absent, but no color or temperature changes were noted in the hand. The clubbing of the fingers and cyanosis of the nails were no longer present. A blood culture taken at that time was sterile.

#### DISCUSSION

Since the over-all mortality rate in bacterial endocarditis has been reduced to between 20 and

30 per cent by the use of antibiotics,<sup>2</sup> and the life expectancy of these patients prolonged, more active measures should be instituted in the treatment of mycotic aneurysms complicating the disease. Although these lesions may develop originally as a result of bacterial invasion of the artery, they should be sterile if the blood stream has been effectively cleared of organisms prior to surgery. Paul, Bland and White<sup>3</sup> and Klein and Crowell<sup>4</sup> reported sterile mycotic aneurysms in patients after treatment with penicillin. The case presented above demonstrates another in which a mycotic aneurysm was found to be sterile after control of the bacteremia by the use of penicillin.

Early surgical extirpation of these lesions should be performed whenever possible because aneurysms of this type are prone either to rupture or to impinge upon adjacent important structures. These complications may be avoided if the clinician is alert to the possibility of their development and institutes proper therapeutic measures before irreversible changes have occurred.

#### SUMMARY

A case of endocarditis due to a Type VIII pneumococcus, with recovery after treatment with penicillin, is reported.

The disease was complicated by the development of a mycotic aneurysm in the first portion of the left brachial artery, with compression and partial paralysis of the median nerve. Surgical removal of the aneurysm, which was found to be sterile at the time of operation, was followed by progressive improvement in the median-nerve function.

Whenever feasible, early surgical excision of an aneurysm of this type is recommended.

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## PRIMARY HEMANGIOENDOTHELIOMA OF THE LIVER IN INFANCY\*

## Report of a Case

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PRIMARY hemangioendothelioma of the liver in infancy is a rare disease as indicated by a review of the literature. In 1933 Kunstadter<sup>1</sup> reported 14 cases, reviewing 13 cases collected from the literature and adding 1 that had come under his observation. Since then Schumann,<sup>2</sup> in 1941, reported 2 additional cases, the first in a six-week-old infant and the second in a thirty-six-hour-old male infant who died of cerebral hemorrhage after delivery. Blauel<sup>3</sup> added 3 cases to the literature — 1 in an infant and 2 in children.

Foote<sup>4</sup> believed that these tumors were peculiar only to infancy. However, they may occur at any age. The patient in the case reported below is the youngest yet observed. The infant at the time of death was nine days old. The next youngest case is recorded by Bondy,<sup>5</sup> in which the patient was three weeks old at the time of death. The oldest recorded case was observed by Miller<sup>6</sup> in a man of seventy-six years.

These tumors are definitely of a malignant character, and are not to be confused with benign hemangiomas of the liver. They have been variously recorded in the literature as angiosarcomas, hemangiosarcomas, endothelioblastoma and so forth. The pathology has been thoroughly described.<sup>1, 4, 6</sup> Grossly, the liver is enlarged, studded with numerous nodules varying in size from a millet seed to masses several centimeters in diameter. These nodules and masses can be seen on the liver surface and within its parenchyma. They present on cut section a dark-red center and an irregular yellowish-gray outer zone. Histologically, these masses consist of blood spaces lined by proliferating endothelial cells in single and multiple layers. In some areas the endothelial cells form papillary ingrowths or proliferate in compact masses.

As further evidence of the malignant character of the tumor, metastases have been observed in a number of cases. Kunstadter<sup>1</sup> reported that metastases were present in 33 per cent of the 14 cases recorded in his paper. Metastases have been observed in the retroperitoneal lymph nodes, vertebrae, skin, ribs, lungs, adrenal glands and spleen. Metastases are more commonly seen in adult cases and more rarely observed in infants, as in the case reported below.

The clinical manifestations are characteristic. There is usually a history of a large abdomen at birth or subsequent rapid abdominal enlargement. Constipation, abnormal stools, vomiting and progressive weight loss are the most frequently observed symptoms. In older patients pain is a common complaint. Pain is most often present in the lumbar, flank or shoulder area.

The physical examination discloses one constant finding. It is the observation of a large abdomen becoming rapidly larger. The enlarged abdomen is usually interpreted as caused by hepatomegaly or right-upper-quadrant masses. Jaundice and ascites are rarely observed.

The course in the disease is rapidly downhill. With the increasing enlargement of the liver, death soon follows. In the majority of the cases reported in infancy the patients died before six months of age. Death is interpreted as due chiefly to liver destruction by the neoplasm, or hastened by any metastases that may be present.

The diagnosis has never been made clinically. Usually the diagnosis becomes apparent after laparotomy or upon post-mortem examination.

## CASE REPORT

J M, a white female infant, was born in the hospital on March 3, 1945, after a normal, spontaneous delivery, with a birth weight of 7 pounds, 9 ounces. Except for several raised moderately large purple masses in the skin of the right shoulder, right ear lobe and both lower extremities, she appeared to be of normal development. The skin masses were considered to be simple hemangiomas.

The mother's past history was noncontributory, except that she was classified as an arrested case of pulmonary tuberculosis.

After delivery the patient did well until the 4th day of life when slight icterus was first noted. On the next day the abdomen became distended. Enemas failed to relieve the distention. On the 7th day of life the enlarged abdomen was flat to percussion, and the superficial abdominal skin veins were distended. It was believed that the abdomen was not tender to palpation and that the liver and spleen were not palpable. At that time the hemoglobin was 72 per cent (Sahli), with no erythroblasts seen in the peripheral blood smear. X-ray examination, consisting of a plain film of the abdomen, revealed a diffuse haziness suggestive of intra-abdominal fluid. The loops of small bowel seemed displaced to the left lower quadrant of the abdomen. An attempt at left paracentesis elicited a negative result, 5 cc of frank blood was obtained upon right paracentesis.

On the eighth day of life the patient appeared acutely ill. The sclerae were definitely icteric. The abdomen was more markedly distended. A surgical consultation on the same day elicited the suggestion that the infant had a congenital liver anomaly, but that the patient's condition was too poor for surgical intervention. The patient died on the following day. The temperature was never elevated. The weight remained stationary.

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Post mortem examination disclosed a well developed, markedly icteric white female infant. Several raised moderately large, purple masses were noted in the skin of the right shoulder, right ear lobe and both lower extremities. The abdomen was distended. The liver edge was palpable just above the right inguinal ligament.

The thymus was of normal size, configuration and location. The lungs were well aerated and of normal configuration. Two hemorrhagic nodules were noted in the left upper lobe.

The heart was enlarged but of normal configuration. When the abdomen was opened the liver was seen to occupy three fourths of the cavity. The liver weighed 420 gm and was of normal configuration. The capsule was smooth and glistening. On section the parenchyma presented a variegated coloring. Deep-purple soft areas were seen interspersed with yellowish-brown and deep gray zones (Fig. 1).

The spleen was moderately enlarged but otherwise normal. The pancreas, adrenal glands and genitourinary and gastrointestinal systems, as well as the brain and pituitary gland showed nothing remarkable.

Sections from the skin masses revealed many markedly distended capillary vessels in the dermis that were closely



FIGURE 1 Tumor Masses in the Liver as Seen on the Cut Surface

packed. There was a scant interstitial stroma. The capillary vessels contained few erythrocytes. The endothelial cells were large but of uniform appearance.

Irregularly outlined masses in the liver (Fig. 2) demonstrated areas of dilated vascular sinuses lined by large endothelial cells, in many of which papillary excrescences composed of massed endothelial cells were seen. In other areas the endothelial cells were present in solid sheets. The endothelial-cell nuclei varied in staining intensity; many were large and vesicular, and others were markedly hyperchromatic. The hepatic lobules revealed marked central necrosis.

Sections taken from the hemorrhagic nodules in the lungs showed intra alveolar hemorrhage.

The final diagnoses were primary hemangioendothelioma of liver and benign hemangiomas of skin.

## DISCUSSION

It is suggested that in cases of infants or young children with rapid abdominal enlargement attributable to hepatomegaly, with or without jaun-

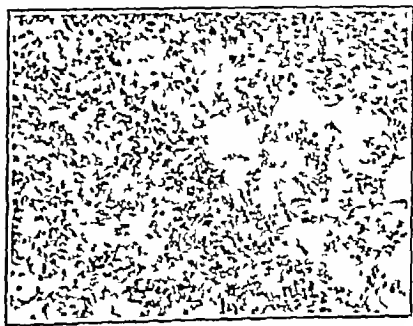


FIGURE 2 Photomicrograph of the Hepatic Neoplasm ( $\times 125$ )

dice, hemangioendothelioma of the liver should be considered as a possible diagnosis.

## SUMMARY

A case of congenital primary hemangioendothelioma of the liver in a nine-day-old infant is reported.

This is the youngest patient with such a disease yet observed.

The clinical and pathological aspects of the disease are reviewed.

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## MEDICAL PROGRESS

### INTERCAPILLARY GLOMERULOSCLEROSIS (Concluded)

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#### RELATION TO HYPERTENSION AND ARTERIOLO-SCLEROSIS

A close relation between intercapillary glomerulosclerosis and arteriosclerosis of the kidney has been obvious to all observers<sup>4, 5, 7, 8</sup>. The two lesions roughly parallel each other, but a sufficient number of exceptions exist to justify the statement that the relation is likely to be coincidental. Although arteriosclerosis cannot be excluded as a contributing factor in bringing about intercapillary glomerulosclerosis, it cannot be regarded as the sole cause. In the age group in which most cases of intercapillary glomerulosclerosis occur, a large percentage of patients reveal marked arteriosclerosis of kidneys with or without the glomerular lesions. Intercapillary glomerulosclerosis has been observed occasionally without significant vascular changes<sup>4, 16</sup>.

The involvement of efferent arterioles in the process of hyalineization seems to be significant.<sup>7, 8</sup> Allen<sup>8</sup> emphasizes the fact that in his experience arteriosclerosis of efferent vessels is absent in nondiabetic cases. Confirmation of this observation on other large series of cases would indeed be desirable. If involvement of the efferent arterioles could be regarded as a specific change in intercapillary glomerulosclerosis, a new avenue of approach would be opened for an explanation of the peculiar glomerular lesion and its clinical counterpart. At present, however, factual observations in this respect are not substantiated in sufficiently large numbers to serve as a basis for a theory of the pathogenesis of intercapillary glomerulosclerosis.

Hypertension, if it occurs in intercapillary glomerulosclerosis, is more likely to be correlated with the accompanying arteriosclerosis. However, hypertension is not observed so constantly as arteriosclerosis in cases of intercapillary glomerulosclerosis. Most of the earlier reports<sup>20-24</sup> show benign and more often moderate arterial hypertension in practically all cases. Cases of malignant hypertension have not come to our attention. Later statistics, however, reveal a considerable number of cases of intercapillary glomerulosclerosis in which hypertension is absent. Laipply<sup>4</sup> found it in only 64.6 per cent, Henderson et al<sup>16</sup> in 60 per cent, and Goodof<sup>3</sup> in only 50 per cent. The low incidence of hypertension cannot fully be explained by the assumption that milder

or diffuse glomerular lesions were included in the statistics since the criteria given in some of them are undoubtedly those of intercapillary glomerulosclerosis of the nodular type. It must thus be concluded that hypertension, though present in a large percentage of cases of intercapillary glomerulosclerosis, — according to Henderson et al<sup>16</sup> twice as frequently as in diabetes without intercapillary glomerulosclerosis, — is not an essential part of the clinical syndrome and is present less frequently than arteriosclerosis.

In summary, arteriosclerosis roughly parallels the severity of intercapillary glomerulosclerosis, but the relation is likely to be coincidental. Involvement of the efferent arteriole is reported to be confined to cases of diabetes. Hypertension most probably related to the vascular rather than the glomerular changes occurs in about 58 per cent of the cases of intercapillary glomerulosclerosis.

#### RELATION TO RENAL IMPAIRMENT, UREMIA AND ANEMIA

Although renal function is markedly impaired in a large percentage of cases, death is just as often due to cardiovascular disease and intercurrent infections. Data concerning the renal function in this condition are still not so complete as may be desired. At least two thirds of the cases show evidence of renal insufficiency as indicated by significantly elevated urea nitrogen or nonprotein nitrogen. Anson<sup>22</sup> reports renal impairment in 66 per cent, Henderson et al<sup>16</sup> in 64 per cent, Porter and Walker<sup>21</sup> in 60 per cent, Siegal and Allen<sup>6</sup> in 80 per cent, and Newburger and Peters<sup>20</sup> in 75 per cent. Death in uremia is reported to have occurred in 17.7 per cent by Laipply<sup>4</sup> and in 33 per cent of 12 cases reported by Chasnoff<sup>23</sup>. The hypochromic microcytic anemia seems to be roughly parallel to the impairment of renal function<sup>10</sup>.

In the remaining cases cerebral accident, cardiac failure, coronary occlusion and other manifestations of cardiovascular lesions are responsible for death. Incidental causes of death are likewise reported in a relatively small percentage<sup>16</sup>. No definite statement can be made regarding the prognosis. Only Spühler<sup>11, 12</sup> and Auroi<sup>10</sup> venture to predict that death may be expected two or three years after the syndrome has fully developed.

In summary, rather scant data concerning the involvement of renal function show impaired function in approximately 68 per cent and uremia in about 25 per cent of patients with intercapillary

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glomerulosclerosis not dying from nonrenal causes. Microcytic, hypochromic anemia seems to parallel renal impairment. According to some authors, death is expected two or three years after the clinical syndrome has fully developed.

#### DIABETES AND INVOLVEMENT OF ISLANDS OF LANGERHANS

Most patients suffered from diabetes of relatively mild degree — as can be expected in the age group from fifty to seventy years in which the majority of these cases occur. It seems to be the rare exception that symptoms and signs of renal involvement antecede detectable diabetes by a few months.<sup>1</sup> Auroi<sup>16</sup> remarks that one should examine for "masked" diabetes in the presence of hypertension and the nephrotic syndrome. Almost always diabetes is recognized prior to the renal disease.<sup>17, 24</sup> In fact, the severity of intercapillary glomerulosclerosis seems to increase with the known duration of diabetes. Goodof<sup>2</sup> reported a consistent increase in severity after a known duration of six years, a statement fully confirmed by Henderson et al.<sup>18</sup> These observations appear to be adequate proof that the glomerular lesions are directly related to diabetes mellitus, though additional factors may be required for its precipitation. The severity of the diabetes, on the other hand, was not found to be parallel to the severity of the glomerular lesion,<sup>18</sup> nor did the treatment for diabetes seem to have any bearing on the renal involvement.<sup>18, 25</sup> It is for this reason that Dolger<sup>26</sup> has justifiably criticized the term "complication" as applying to vascular or glomerular lesions in diabetes. Since even the control of diabetes over a period of years cannot prevent the development of vascular and glomerular lesions, these should be considered as manifestations of the same basic disorder rather than "complications" of diabetes.

There is no direct relation between intercapillary glomerulosclerosis and hyalinization of the islands of Langerhans.<sup>2, 6, 18, 17</sup> Henderson et al.<sup>18</sup> conclude from their data that intercapillary glomerulosclerosis is not a more reliable criterion for post-mortem diagnosis of diabetes than the hyalinization of the island of Langerhans, in contrast to Lippay,<sup>4</sup> who considers intercapillary glomerulosclerosis the more reliable criterion.

Thus, in the great majority of cases, diabetes antecedes intercapillary glomerulosclerosis. The latter increases in severity after a known duration of diabetes of six years. Treatment for diabetes has no bearing on the development of intercapillary glomerulosclerosis. There is no consistent relation between intercapillary glomerulosclerosis and hyalinization of the islands of Langerhans.

#### RELATION TO RETINOPATHY

Retinal changes have frequently been mentioned in reports of cases of intercapillary glomerulo-

sclerosis, but only during the past year has the relation between retinopathy and intercapillary glomerulosclerosis been made the subject of specific studies. Henderson and his associates<sup>17</sup> found that retinopathy was present in 68.8 per cent of cases of diabetic intercapillary glomerulosclerosis, in contrast to 22.8 per cent of cases of diabetes without intercapillary glomerulosclerosis. Further analysis revealed two points of significance. In the first place, the great majority of cases showed a more complex type of retinopathy, the purely hypertensive type was present in only 1 out of 32 cases. Hence, retinopathy associated with intercapillary glomerulosclerosis almost always includes changes attributable to diabetes.

Secondly, in the subdivision and grading of the retinal changes, it was noted that the incidence of more complex and advanced types was higher in cases of diabetes with intercapillary glomerulosclerosis — those showing hemorrhages only or hemorrhages with punctate exudates were less frequently associated with intercapillary glomerulosclerosis. The authors concluded that the advanced type of diabetic retinopathy is more or less regularly associated with intercapillary glomerulosclerosis.

Dolger,<sup>1</sup> who based his report on a purely clinical study of a large number of patients, including 55 cases of juvenile diabetes, found that 50 per cent of his patients exhibited hypertension and albuminuria at the time of earliest retinal hemorrhages. His investigation correlates retinopathy with the clinical syndrome of diabetes, hypertension and albuminuria, assuming the identity of this syndrome with intercapillary glomerulosclerosis. This identity, however, is still being discussed. His statistics show the remarkable fact that there is practically no difference in the onset of retinopathy in the third and fourth decades of life, appearing thirteen years after onset of diabetes in each group of patients and being associated in 50 per cent with hypertension and albuminuria regardless of the age group. In patients of the fifth decade evidence of "accelerated vascular degeneration" with "earlier appearance of all abnormal findings" occurs at an average of ten years after onset of diabetes.

His observations show that retinopathy presages the vascular lesions and also, by implication, intercapillary glomerulosclerosis.

In summary, advanced retinopathy, specifically of the diabetic type, is more or less regularly associated with intercapillary glomerulosclerosis and should therefore be added to the complex clinical syndrome associated with the glomerular lesion. It precedes the renal changes and is more closely related to the diabetes than to the vascular or glomerular disease.

#### HISTOGENESIS

A number of notable contributions to morphologic details have been published in the litera-

ture,<sup>7, 9, 26, 27</sup> but this report concerns only studies that are pertinent to the problem of histogenesis.

The hyaline deposits in the glomeruli in hematoxylin-stained and eosin-stained sections often resemble amyloid, but do not possess its staining characteristics. Some authors believe it to be amyloid-like<sup>28, 29</sup>. Occasionally, it stains with Congo red, but Fahr,<sup>9</sup> who erroneously classified some of his earlier cases originally as amyloidosis, admits the lack of specificity of this staining reaction, and he, like most authors, concludes that the material cannot be identified as amyloid.

The glomerular changes, though often not in direct continuity with the hyalin in arterioles, were most commonly seen in senile kidneys and therefore originally conceived as aging or "axial" degeneration. In only two conditions, however, was this process observed in an extremely striking degree—namely, in diabetes and chronic intracapillary glomerulonephritis. Almost all subsequent observers have agreed with the descriptive identification of the lesion. Many have accepted the concept of intercapillary glomerulosclerosis, but some authors, notably Allen,<sup>8</sup> Laipply<sup>4</sup> and Bell<sup>7</sup> have disagreed with the assumption that the changes take place primarily in the intercapillary connective tissue. They have come to the conclusion that the lesions are produced by a splitting of the capillary basement membrane. Both Allen<sup>8</sup> and Bell<sup>7</sup> agree in their most important argument—that splitting and fraying of the inner basement membrane can be observed in early lesions.

In an analysis of the early lesion<sup>1</sup> it was found very difficult to determine accurately the origin of frayed fibers "splitting off" or "merging with" the capillary basement membrane. A special stain was devised for this purpose,<sup>2</sup> but the authors were finally convinced that conclusions regarding the origin of these fibers had to be reached by inference rather than by indisputable observation. All observers agree that the first appearance of fibers and hyalin occurs at the "inner" basement membrane—that is, the segment of the capillary wall that is situated toward the center of the lobule. To explain this position, which is characteristic for the early lesion, as well as its mode of extension, it was assumed that the original changes take place in the intercapillary connective tissue, the only available anatomic structure that could account for the peculiar topographic distribution.

To illustrate the complexity of this problem we refer to a recent study of the glomerular basement membrane by McManus.<sup>30</sup> His periodic acid stain reveals that the basement membrane of the arterioles is lost as the capillaries of the tuft form in the glomerulus. The basement membrane of capillaries appears to derive from Bowman's capsule, leaving points of reflection or the intercapillary space. This space usually appears empty, but very rarely contains cells of the "mesangium." In glo-

merulosclerosis, glomerulonephritis and eclampsia the space shows up better than it is usually seen.

Bell<sup>7</sup> does not accept the existence of intercapillary connective tissue in the periphery of the glomerular lobule. Zimmermann,<sup>31</sup> however, has convincingly demonstrated its occurrence in the normal glomerulus. The connective tissue is thickest at the pole, thinning gradually toward the periphery. We do not believe that it is possible to determine in any given section just how far out into the lobule it extends. Allen<sup>8</sup> speaks of a "mantle" surrounding the capillary loop corresponding to the adventitia. This tissue may be indistinguishable from the basement membrane and may, according to Allen,<sup>8</sup> take part in the process of hyalinization, although the lesion primarily involves the basement membrane.

Fahr<sup>9</sup> has recently proposed a new hypothesis concerning the histogenesis of intercapillary glomerulosclerosis. He compares the histologic structure of the glomerulus with that of the tubules. The latter are composed of epithelium, tunica propria and interstitial tissue, separating the tubules from the adjacent capillary membrane and its endothelium. He conceives of the glomerular tuft as a structure in which the tunica propria, the interstitial tissue and the capillary membrane have merged into one membrane. He therefore concludes that two forms of glomerulosclerosis can be distinguished—the capillary form, generally identical with arteriolosclerosis, and the extracapillary form, genetically analogous to hyalinization of the tunica propria of the tubules. It is the latter form that is identical with the lesion under consideration.

The terms extracapillary glomerulosclerosis (Fahr<sup>9</sup>) and mural glomerulosclerosis (Allen<sup>8</sup>) represent difference in interpretation, not in observation. We prefer to maintain the original term because it appears to be the most descriptive one, and because most authors agree that the fully developed lesion creates the impression that it is situated between the capillaries.

In summary, the concept that the glomerular changes originate from intercapillary connective tissue is reached by inference, mainly on the basis of its peculiar topography. There is, however, no unanimity of opinion in this respect. Various theories have been proposed. It is suggested that the term intercapillary glomerulosclerosis be retained since it has served well for the purpose of descriptive identification.

#### INTERCAPILLARY GLOMERULOSCLEROSIS AS A CLINICOPATHOLOGICAL ENTITY

The histologic segregation of the first 8 cases<sup>1</sup> seemed to be justified in part by the fact that certain clinical features were associated with the disease. It was then stated that a previous history of diabetes, edema of the nephrotic type and gross albuminuria were characteristic. Hypertension was



frequently present in cases associated with renal decompensation. Twelve years later Bell<sup>1</sup> concluded that clinical symptoms and signs of diabetes seldom warrant the diagnosis of intercapillary glomerulosclerosis. There are no definite clinical features, he states, by which diabetes with intercapillary glomerulosclerosis can be distinguished from diabetes without intercapillary glomerulosclerosis. A survey of the literature has shown that neither of the statements is entirely correct.

The accumulated experience since the first publication has shown that the complete clinical syndrome occurs in a relatively small percentage of cases of intercapillary glomerulosclerosis. With the exception of chronic glomerulonephritis, it can be stated that diabetes occurs in almost all cases of intercapillary glomerulosclerosis. Hypertension is found in approximately 60 per cent. Significant albuminuria is found in the majority of cases (approximately two thirds), edema of the nephrotic type in less than 10 per cent, impairment of renal function in from 50 to 75 per cent, uremia in roughly 20 per cent, and retinopathy in 86 per cent of cases with the advanced lesion. It is therefore correct to state that there are no definite clinical features to establish the diagnosis of intercapillary glomerulosclerosis. They are certainly not so definite as the histologic findings. Intercapillary glomerulosclerosis shares this fate with many other distinct pathologic conditions of inner organs.

Before final judgment is cast, two factors should be evaluated in future studies. The first is that a complete clinical investigation should be correlated to histologic findings, with specific reference to the degree and type of the lesion. Many of the older reports are not entirely conclusive in this respect. From some of the recent studies it seems likely that the severe, nodular type shows a closer and more consistent relation to the clinical symptomatology than the mild or diffuse type. Mild glomerular lesions are less apt to give rise to any component of the complex clinical manifestations, whereas the more severe lesions manifest themselves more completely.

Secondly, it is conceivable that the preponderance of the various components depends significantly on the age distribution. Spühler<sup>11, 12</sup> has suggested dividing the clinical picture into three types: diabetes in youth, beginning with nephrosis and later showing elevation of blood pressure and symptoms and signs of nephrosclerosis, diabetes in middle age, in which vascular and nephrotic syndromes develop simultaneously, and diabetes in old age, in which nephrosclerosis is predominant, often without the nephrotic syndrome.

Spühler<sup>11, 12</sup> has gained this impression from observations of his own relatively small series of cases. Discrepancies concerning the frequency of certain components of the clinical symptomatology may be solved if Spühler's concept can be

larger series. Most previously reported statistics do not lend themselves adequately to a respective analysis.

The question whether or not intercapillary glomerulosclerosis constitutes a clinicopathological entity cannot be answered with finality. Even though relatively rare, exceptions have been observed cases in which diabetes was absent, although the renal lesions were fully developed. It is also undoubtedly true that identical lesions occur in glomerulonephritis without diabetes in a significant number of cases. A similar situation, however, exists in many other "diseases" in which a definite pattern of clinical signs and symptoms is correlated to distinct pathological findings, although the same histologic change may occur in a different set of circumstances and may result from different etiologic factors. Should we abolish the concept of malignant hypertension because the same histologic changes in arterioles occur in periarteritis nodosa and lupus erythematosus?

Whether we look upon intercapillary glomerulosclerosis as a clinical entity depends to some extent on the approach to this question. The clinician, observing a diabetic patient who develops gross albuminuria, nephrotic edema, hypertension, impairment of renal function and retinopathy has in the past regarded such a condition as coincidental or as a concurrence of two or three different diseases.<sup>6, 11, 12</sup> He is now in a position, however, to predict with reasonable certainty a pathologic lesion in the kidney that is directly related to the basic metabolic disorder, — the diabetes, — merely constituting a variant of its manifestation. Obviously, there can be no accurate correlation between the histopathological findings in the glomeruli and the clinical symptoms. This is due to the fact that there is no way of determining accurately how many glomeruli are involved or to what degree protein metabolism is compromised by protein loss on the one hand and disturbance of protein synthesis on the other. It is obvious that the latter factor is considerably disturbed in patients with glomerulonephritis with the nephrotic syndrome, and apparently the same statement applies to the condition under discussion. One can say, however, that in a patient fifty or more years of age with chronic diabetes, nephrotic edema and albumin in the urine with high blood cholesterol, one can safely make the diagnosis of intercapillary glomerulosclerosis with approximately 100 per cent accuracy. Glomerulonephritis is rarely a problem in patients of this age group. Repeated Addis counts noting the number of red cells and casts excreted each twenty-four hours will certainly enable one to make the diagnosis of glomerulonephritis, for in that condition red cells will appear in pathologic numbers in contrast to lack of hematuria of significant degree in intercapillary glomerulosclerosis.



The diagnosis of this disorder carries with it a grave prognosis, which cannot be influenced by treatment of diabetes. It is true that the clinical diagnosis of intercapillary glomerulosclerosis is not infallible, but the "presence of advanced lesion can be predicted with considerable certainty."<sup>16</sup> It is inferred from the study of the literature that most authors have shared this experience. The difficulty in recognizing earlier or less advanced lesions does not interfere with the concept of intercapillary glomerulosclerosis as a clinicopathological entity. It should rather constitute a challenge to a search for better criteria for early diagnosis.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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### CASE 34261

#### PRESENTATION OF CASE

*First admission.* A thirty-year-old Negro entered the hospital because of weight loss and flank pain.

Six weeks before admission the patient developed a urethral discharge three days after suitable exposure. This was diagnosed as gonorrhea by his physician, and treatment consisted of four injections of penicillin followed by three tablets of sulfadiazine every four hours for four days. He stopped "half-way through the treatment" because of malaise and feverishness. Two days after the sulfadiazine was stopped he became oliguric, and two days later anuric. The anuria lasted for two days and was succeeded by polyuria, nocturia, cloudy urine and flank pain. Over the next four weeks the last two symptoms gradually subsided but the polyuria, nocturia (three times) and general malaise continued and the patient lost 25 pounds. There was no dysuria, hematuria or colicky pain. Four days before admission he noted the onset of continual nausea, occasional vomiting, cramping of the fingers and blurring of vision.

Twelve years before admission the patient had contracted pulmonary tuberculosis and spent three years in a sanatorium.

Physical examination showed a well developed, thin, pale Negro. The left chest moved poorly with respiration, and there was decreased resonance, breath sounds and spoken voice over the left upper lobe. Bilateral costovertebral-angle tenderness was present.

The temperature, pulse and respirations were normal. The blood pressure was 100 systolic, 60 diastolic.

The hemoglobin was 12 gm per 100 cc, and the white-cell count was 7100. Urinalysis showed a specific gravity of 1.010, a ++ test for albumin, no red cells and 5 to 10 white cells per high-power field. A culture of the urine grew a nonhemolytic streptococcus and *Staphylococcus albus*. Repeated sputum examinations were negative for acid-fast bacilli. The nonprotein nitrogen was 100 mg, and the total protein 4.1 gm per 100 cc, with an albumin-globulin ratio of 0.9, the serum calcium was 7.7 mg and the phosphorus 4.6 mg per 100 cc, and the carbon dioxide was 19.3 milliequiv per liter. There was no sulfonamide in the blood. A phenolsulfonephthalein test showed less than 5 per cent excretion of the dye in two hours. A blood Hinton test was negative. The basal metabolic rate was -26 per cent. X-ray films of the chest showed findings consistent with an old pneumothorax on the left side and resulting pleural thickening. There was no evidence of activity. A plain film of the abdomen displayed no unusual features. The kidney shadows were incompletely visualized.

The patient improved somewhat on a low-sodium, normal-protein diet and forced fluids. The nonprotein nitrogen fell to 74 mg and the phosphorus to 4.6 mg per 100 cc.

The patient was discharged to be followed in the Out Patient Department

**Second admission** (two months later) He did well at home for several weeks but then noted the onset of malaise, intermittent ankle edema, nausea, occasional vomiting and a chronic cough productive of whitish sputum. Left costovertebral angle and flank pain persisted, as well as nocturia (two or three times). There were no chills, fever, dysuria or hematuria.

Physical examination showed, in addition to the findings on the first admission, generalized, firm, mobile, discrete, nontender lymphadenopathy and minimal pitting edema of the legs and ankles.

The hemoglobin was 8.5 gm, and the white-cell count 9600. Urinalysis showed a specific gravity of 1.012, a +++ test for albumin and numerous white cells. There was no growth on culture of the urine. The nonprotein nitrogen was 61 mg, the total protein 5.7 gm (albumin-globulin ratio of 0.8), the serum calcium 8.5 mg, and the phosphorus 4.5 mg per 100 cc. Two Congo-red tests showed respectively 41 per cent and 70 per cent retention of the dye in the serum. In an x-ray film of the chest no change was seen in the left lung, whereas in the right there was an area of increased density at the right base and a similar area previously noted at the right hilus was somewhat larger.

Very little change was noted in the patient's clinical condition or laboratory data during this hospital stay, and he was discharged on the seventeenth day.

**Final admission** (four months later) The patient did fairly well on bed rest at home for two months, but then coincident with his getting up he suffered a return of the old symptoms — malaise, anorexia, nausea, vomiting and pain in the left flank, radiating around to the groin. All these progressed and as the vomiting became worse the urine output decreased. During the week before admission he noted facial edema in the mornings and occasional twitching of the legs.

Physical examination showed a thin, moderately dehydrated, sleepy, yet well oriented man lying flat in bed. Aside from the patient's general condition the physical findings had not changed.

The temperature, pulse and respirations were normal. The blood pressure was 95 systolic, 60 diastolic.

The hemoglobin was 8 gm, and the white-cell count 13,300, with 92 per cent neutrophils. Urinalysis showed a specific gravity of 1.010, a +++ test for albumin and 1 or 2 red cells and 0 to 2 white cells per high-power field. Again, urine cultures grew nothing. The nonprotein nitrogen was 176 mg, the total protein 4.0 gm (albumin-globulin ratio of 0.7), the serum calcium 5.3 mg, and the phosphorus 16.6 mg per 100 cc. The carbon dioxide was 24.9, the chloride 86, the sodium 125,

and the potassium 7.3 milliequiv per liter, and the cholesterol 208 mg per 100 cc. X-ray films of the chest and abdomen showed no essential change except for disappearance of the area of increased density at the right base.

The patient gradually lapsed into coma, the temperature became subnormal, reaching a low point of 93°F (rectal), the pulse remained in the neighborhood of 70 to 80, and the respirations varied between 12 and 20. Muscular twitching was prominent. He was given plasma, physiologic saline solution, sodium lactate and desoxycorticosterone acetate. In spite of this the serum sodium fell to 108, the carbon dioxide to 15.5, and the chloride to 57 milliequiv per liter. The nonprotein nitrogen rose to 240 mg per 100 cc. Terminally, respirations became slow and deep, the pulse was slow, and the blood pressure fell to 60 systolic, 20 diastolic. He died quietly on the fifteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

**DR. JACOB LERMAN:** Two Congo-red tests showed respectively 41 per cent and 70 per cent retention of dye in the serum.

That is an important statement. These tests were done in a short space of time. Therefore, I must accept the 41 per cent retention of the dye as more valid than the 70 per cent, because the previous uptake of Congo red by the liver cells would have given falsely high results in subsequent tests.

On the first admission we find that the patient reacted to sulfonamides, resulting in renal shutdown. Most likely this was due to the deposit of crystals in the tubules rather than to a sulfonamide type of acute nephritis. In the course of the following four weeks he began to develop evidence of marked renal failure. Because of the short duration one must assume that this man had underlying renal disease. Otherwise, it is hard to explain the rapid progression of renal failure. He began to show polyuria, nocturia, malaise, weight loss and so forth. He began to retain phosphorus and developed symptoms of tetany. The laboratory data subsequently verified this — that is, the blood calcium dropped. We also learn that he had had pulmonary tuberculosis in the past.

He showed, on examination, bilateral costovertebral angle tenderness, which we assume was due to infection in the kidneys. It might have been due to residue of crystals in the tubules, although that is not likely. It was about four weeks from the onset of the first damage by sulfonamides, and we would expect no more physical signs at that time. The urinary findings favor renal infection. In addition, he began to show evidence of acidosis. The reduced carbon dioxide was probably the result of damage to the ammonia-producing mechanism, so that he was losing a great deal of

base The basal metabolic rate was -26 per cent I assume that it was taken because someone suspected lipid nephrosis Actually, we do not have much evidence for lipid nephrosis here Later on, we learn that the cholesterol was normal On the second admission he developed a chronic cough and further changes in the lung seen on x-ray examination It might be well to look at the films

DR STANLEY M WYMAN The old thickened pleural line is seen overlying a partially collapsed left lung, and some calcification is seen in this area, probably lying posteriorly and not in the lung itself There are a few small mottled areas of calcification in the right upper-lung field The heart is drawn toward the left The left costophrenic angle is obliterated by the old pleuritis There is an indefinite shadow of density overlying the right hilus, which persists on the next examination and seems still larger about two months later At that time there is a small area of hazy density in the right costophrenic angle The last film of the chest shows a decrease in size of the round area of density over the right hilus The left chest shows no definite change at this time The two films of the abdomen outline very poorly the kidney shadows I think the right kidney may be a little large The left I cannot adequately see The liver does not appear enlarged, the spleen cannot be outlined

DR LERMAN Are there any renal calculi?

DR WYMAN No, I do not see any in these films I also do not see any unusual soft-tissue masses

DR LERMAN There is mention of a shadow at the right base, which decreased in size

DR WYMAN Yes, this is the one in the right lower-lung field that disappeared in four months The second shadow had become somewhat smaller

DR LERMAN On seeing the x-ray films, I wonder if one might conjure up such a diagnosis as cancer of the lung, particularly lymphoma The disappearance of this shadow and the changes in the mediastinum tend to rule out this diagnosis

On the final admission he developed dehydration and marked chemical changes in the blood, which I shall discuss in a minute

It seems to me, from the evidence available, that there was an underlying chronic pyelonephritis, resulting in renal failure In addition, the evidence seems to point toward amyloid disease, particularly the high uptake of Congo red He had a good background for amyloid disease—namely, long-standing pulmonary tuberculosis Unfortunately, we find no mention of the size of the liver or spleen, although Dr Wyman has just said that the liver was normal in size and that the spleen could not be visualized Is that correct?

DR WYMAN So far as I can see

DR LERMAN The evidence of tubular damage we have obtained from the history also favors amyloid nephrosis Mention is made of generalized lymphadenopathy in addition to the nodes in the

mediastinum The only conclusion that I can make is that this was not lymphoma, but rather tuberculous nodes In addition, he had evidence of clinical tetany With a low calcium and high phosphorus of this degree, we must assume that the pathologist will find secondary hyperplasia of the parathyroid glands

How can we explain the dramatic change in the blood chemical findings? I refer to the very low levels of blood sodium and chloride and the high blood potassium These raise the question of Addison's disease We have here a possible background for Addison's disease—namely, long-standing pulmonary tuberculosis Therefore, damage to the adrenal glands is possible There is no mention and we see no evidence of calcification of the adrenal glands Although this does not rule out Addison's disease, it certainly does not favor it The history in itself does not give clues to any previous episodes of adrenal failure This patient had plenty of opportunity to develop adrenal failure, particularly following the reaction to sulfonamides However, there is no evidence of adrenal failure at that time As I interpret the x-ray films he had a normal-sized heart Do you agree, Dr Wyman?

DR WYMAN Yes

DR LERMAN In general in Addison's disease one finds a rather small heart I think one can account for the marked changes in the blood chemical findings by the fact that the patient was severely dehydrated He had lost a good deal of sodium and chloride by vomiting and a good deal of base through the kidneys as a result of damage to the ammonia-producing mechanism Also, the failure of the blood to improve even transiently from treatment with salt and desoxycorticosterone acetate is against the diagnosis of adrenal failure

One thinks also of renal tuberculosis as a complicating factor here We have not enough evidence for it There was no significant hematuria, and nothing is mentioned in the examination of the urine to give a positive clue So I have to rule it out

DR F DENNETTE ADAMS How do you account for the pain? It worries me The patient came in complaining of pain

DR LERMAN I thought we might find evidence of renal calculus However, the absence of hematuria and these x-ray films make one believe that there is not enough evidence for renal calculus Perhaps the patient passed a stone He also complained of pain in the flank on the second admission It could be explained by pyelonephritis, since there is evidence of renal infection

DR ALFRED KRANES Do we know how long he had the low-sodium diet? Was he on it during the entire period?

DR ERNEST CRAIGE About four months

Dr. KRANES The reason I ask is that this type of death has been described in people with renal disease on a low-sodium diet and is something that should be borne in mind. The clinical findings of so-called sodium-depletion shock resemble acute renal insufficiency. In addition to the mechanism that Dr. Lerman mentioned, it may be partially responsible.

Dr. EDWARD F. BLAND He did not respond promptly to cessation of the low-sodium regime.

Dr. TRACY B. MALLORY On the last entry he received adequate saline solution.

Dr. LERMAN I had assumed that he was on the low-sodium diet only on the first admission, since subsequently the diet was not mentioned. I had supposed that later he was placed on a normal diet — apparently this is not so.

Dr. CRAIG He was carried at home on a moderately low-sodium diet. During the last admission he was given a great deal of salt and sodium lactate. He failed to improve, however.

The opinion on the ward on the first admission was that he had a sulfonamide nephrosis, but that diagnosis was dropped when he failed to recover after three weeks. Later on there was increasing evidence of chronic nephritis and on the last admission the diagnosis was chronic glomerulonephritis.

Dr. MALLORY On the first entry he was presented at Grand Rounds, and I saw him on that occasion. The service at that time seriously considered the possibility of a sulfonamide nephrosis. So far as I know, no such case has ever been seen to progress to a chronic renal lesion — the patients either recover or die in the acute stage. It became obvious as time passed that some other renal condition must have been present.

Dr. KRANES The other thing I have in mind is the question of amyloidosis. This patient had the setup for amyloidosis, with the long-standing tuberculosis, but I do not believe the evidence in the record justifies one in making that diagnosis. The retention of 41 or even 70 per cent, although it may indicate amyloidosis, does not necessarily do so. An interesting series of studies was carried on in New York on this problem, and not infrequently the retention was as high as 80 and 90 per cent, not followed necessarily by the finding pathologically of amyloid disease.

Dr. BLAND What were your final diagnoses, Dr. Lerman?

Dr. LERMAN Chronic pyelonephritis, amyloid disease, old pulmonary tuberculosis and tuberculous adenitis.

Dr. MALLORY Are you satisfied on the films that that is thickened pleura?

Dr. WYMAN The appearance has not changed since the first examination — over a period of seven months. It is probably thickened pleura in addition to old empyema and old fluid. One

cannot say roentgenologically whether it is solid tissue or encapsulated fluid. The hilar masses I cannot explain except to call them enlarged lymph nodes. I cannot exclude entirely a tumor at the hilus — actual new growth.

#### CLINICAL DIAGNOSIS

Chronic glomerulonephritis

#### Dr. LERMAN'S DIAGNOSES

Chronic pyelonephritis

Amyloid disease.

Chronic pulmonary tuberculosis

Tuberculous adenitis

Addison's disease?

#### ANATOMICAL DIAGNOSES

Pulmonary tuberculosis, chronic, inactive

Oligothorax

Amyloidosis of kidneys, spleen, and adrenal glands

Pulmonary edema, acute

Psoas abscess, tuberculous

#### PATHOLOGICAL DISCUSSION

Dr. MALLORY At autopsy the left lung was markedly compressed by a large, very thick-walled sac, and when we cut into it we found that the center consisted entirely of oil. Eventually, we were able to get a history from the tuberculosis sanatorium in which the patient had been that they had injected demerol in oil during his stay there, and the oil had evidently persisted ever since. There was at least 300 cc. The remainder of the cavity consisted of cheesy, necrotic material, completely unidentifiable under the microscope. We found in the lung a number of scattered calcified foci evidently representing healed tuberculosis, but no evidence of activity.

There was a psoas abscess. The liver was completely normal. The spleen was firm, quite pale and characteristic of amyloid. The kidneys were slightly enlarged, had smooth surfaces, were of waxy consistence and, again, were grossly consistent with amyloid. Nothing remarkable was noted about the adrenal glands on gross examination, except that they were heavy, weighing 26 gm. Microscopically, there was evidence that the adrenal substance was almost completely replaced by amyloid. So I think that the patient probably had Addison's disease, based not on tuberculosis but on the amyloid involvement of the adrenal glands. The lesion in the kidney likewise proved to be pure amyloid, with no evidence of nephritis.

CASE 34262

#### PRESENTATION OF CASE

A fifty-four-year-old man was admitted to the hospital with a mass over the right anterior chest.

Ten months before admission the patient experienced a sharp pain over the right anterior chest,

which he attributed to trauma. The pain soon disappeared, and he forgot all about it. Two months prior to admission, following a routine x-ray examination of the chest, a tumor involving the right fifth and sixth ribs was discovered. At that time the patient was in another hospital undergoing treatment for rheumatoid arthritis, involving the cervical spine, the knees and the right middle finger, of about five years' duration.

Physical examination revealed a well developed and well nourished man. Evidence of rheumatoid arthritis, without acute activity, was present in the cervical spine, the right knee and the right middle finger. A tender, questionably nodular mass was present over the right fifth and sixth ribs in the midclavicular line. Auscultation disclosed a Grade I systolic murmur at the base of the heart.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood showed 13.2 gm of hemoglobin and a white-cell count of 8500, with 63 per cent neutrophils, 26 per cent lymphocytes, 7 per cent monocytes and 4 per cent eosinophils. The urine was normal. The sedimentation rate was 18 mm in 15, 42 mm in 30 and 52 mm in 45 minutes and 54 mm in 1 hour. X-ray examination revealed a destructive process involving the anterior axillary portion of the right sixth rib over a distance of approximately 7 cm. There appeared to be a soft-tissue mass surrounding this area. The trabeculae were increased in prominence, and the rib appeared expanded and destroyed. The extreme anterior tip of the rib was spared. No other definite lesions were seen in the remaining ribs, the thoracic or lumbar spine, pelvis, upper humeri or femoral shafts. There were degenerative changes about the lower thoracic and lumbar vertebrae and about the hip joints. There was some kyphosis of the upper thoracic spine. The left kidney was poorly visualized on the films of the spine, and appeared grossly normal, the right kidney was not adequately seen.

On the second hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR WILLIAM S. CLARK. It seems reasonable to accept the diagnosis of rheumatoid arthritis in this patient because of the fact that he had had symmetrical joints involved, and because the distribu-

tion of joint involvement is quite consistent with that diagnosis. It should be pointed out here that this man was apparently in good health at the time of admission. Even with rheumatoid arthritis he was in a good state of nourishment, and except for the rapid sedimentation rate he had very little evidence of constitutional disease.

To learn more about the rib lesion and also to find out what we can about the rheumatoid arthritis let us look at the x-ray films. First of all may we see the films that suggest the presence of arthritis, particularly those of the sacroiliac region?

DR JAMES J. MCCORT. There is no evidence of arthritis in the sacroiliac joints. I do not have the films of the other bones that showed the arthritis. These are the films that you have already seen, and the mass is apparent on the routine chest film extending into the pleura and on this other film one can see the mass extending outside the chest wall. There is definite destruction of the right sixth rib in the anterior axillary line. The rib is destroyed in that area. The lesion is more or less destructive, and there is no new bone formation, no spicule formation in the soft tissue and no periosteal reaction over the edges of the rib. The extreme anterior segment of the rib is intact. The soft-tissue tumor is smooth and shows no calcification within it.

DR CLARK. How about the trabeculae that are described in the protocol?

DR MCCORT. I would interpret it as meaning that the smaller trabeculae were destroyed so that the remaining trabeculae stood out, rather than thinning per se of the trabeculae.

DR CLARK. There were no trabeculae coursing through the tumor apparently. I think with the history of joint involvement that one might consider the possibility of some new bone formation and perhaps fuzziness along the margins of the sacroiliac joints. The evidence is certainly not striking, however.

DR MCCORT. We would like better films to determine that.

DR CLARK. First of all I do not believe we need consider this lesion of the rib as being one of the manifestations of rheumatoid arthritis. I know of no such destructive lesion of bone that occurs in the course of that disease, though we have to consider that (in the course of rheumatoid arthritis) he had developed an additional lesion of the rib. The first thing we should decide is whether this

was an inflammatory lesion or a tumor. There is very little in the protocol to help decide that. The patient was in apparent good health, the white-cell count showed no evidence of infection and there are no data to support the thesis that this might have been a granuloma. So I am going to discard that possibility, although the evidence against it is not too strong, and conclude that it was a tumor.

There are very few primary tumors so far as I know that involve the ribs. We will consider some of these, perhaps in an encyclopedic fashion, because I suppose any one of them could be the final diagnosis. Perhaps one of the more common rather benign tumors that involve the ribs is a chondroma. I suppose such a tumor could fit this picture, but the chondroma as I understand it is usually related to the small joints of the thoracic cage and since a portion of the rib adjacent to the costochondral junction is spared, I think we can discard that possibility. Giant-cell tumors of the rib are reported, and I inquired about the trabeculae because I thought this tumor might have had the appearance of a giant-cell tumor. In this age group I think that would be something to which one should give a little more than the usual amount of consideration, but we really have nothing to support it from the x-ray appearance and as I understand it the x-ray findings are reasonably characteristic in giant-cell tumors. A Ewing tumor is unlikely in a person of this age, particularly with the history of a relatively long pain-free period following the onset of the lesion. The pain in Ewing's tumor usually increases with time, and the tumor may also be accompanied by secondary constitutional manifestations not present here, particularly leukocytosis and fever. The other thing about Ewing's tumor that rules it out fairly well is the absence of new bone formation.

We have to consider the possibility of multiple myeloma although solitary lesions in myeloma are extremely rare. The x-ray films show no evidence of additional lesions. On the basis of the improbability of finding one solitary lesion representing myeloma we can discard that diagnosis. Another point against multiple myeloma is the fairly normal peripheral blood count. I think even if this were a solitary lesion of that nature there would also have been some infiltration of the bone marrow resulting in anemia. Hodgkin's granuloma also is seen under such circumstances, but I think rarely when it is the first manifestation of

disease. Again, the apparent well-being of the patient and the lack of abnormalities in the peripheral blood are against that diagnosis. I believe if there were such a lesion of bone whereby the disease would be noticed, there would also have been infiltration of the bone marrow. Incidentally, the eosinophil count of 4 per cent is quite consistent with rheumatoid arthritis—it is not really an abnormal finding. We really cannot find any good evidence to support any of these diagnoses. There is nothing in the protocol that indicates that this man had a tumor elsewhere and that this was a metastatic lesion. The fact remains that by far the most common tumors that occur under such circumstances are metastatic lesions.

It is true, again, that the patient was in apparent good health, and the thesis that he had a malignant tumor elsewhere metastasizing to the rib might not hold up. There is no evidence of involvement of systems other than what is noted about the kidneys—namely, that they were poorly visualized. I do not consider that of any value in making this type of decision, and the urine was normal. Purely on the basis of probability, as well as the fact that this was a destructive lesion, I prefer to consider a metastatic tumor of the rib. If I were looking for a primary site, I suppose it would be best to consider the thyroid gland or the stomach or the kidney. There is no evidence that he had carcinoma of the stomach, and again the anemia may be evidence against that diagnosis. The thyroid gland was not reported as abnormal. So I shall say that this was a metastatic tumor of the rib, possibly from a hypernephroma or renal-cell carcinoma.

#### CLINICAL DIAGNOSIS

Metastatic carcinoma of rib, of thyroid or renal origin

#### DR. CLARK'S DIAGNOSIS

Metastatic tumor of rib, possibly hypernephroma or renal-cell carcinoma

#### ANATOMICAL DIAGNOSIS

Metastatic renal adenocarcinoma

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: It was decided to examine the rib lesion. One of the problems we have

to face in the laboratory almost every day is that of attempting to give the clinician a lead where to seek the primary tumor from the microscopical appearance of metastasis. A large part of the time we are entirely unable to help him, but in this case, we were dealing with one of the histologically most characteristic neoplasms, a clear renal-cell carcinoma, and it was possible to make a flat-footed diagnosis from the biopsy of what is ordinarily called hypernephroma. The patient was then turned over to Dr Leadbetter.

DR WYLAND F LEADBETTER. On the basis of the biopsy report we assumed that the patient had a renal-cell carcinoma. A retrograde pyelogram showed characteristic changes in the calyces of the right kidney compatible with the diagnosis of renal-cell carcinoma. No other metastatic lesions were found, so we thought that it was worth while to remove the right kidney if the lesion was operable. Later on it was planned to remove the metastatic lesion in the ribs. That was done — a transperitoneal right nephrectomy. We were able to remove the kidney together with the fat and the fascia. We did not see the kidney at any time during the operation. The vessels were tied, and the kidney and enveloping fascia were shelled out en masse. The operation was satisfactory, and the patient made a good recovery. Dr Grantley W Taylor is now going to remove the metastatic lesion in the rib.

DR MALLORY. We have an occasional case in which very notable remissions have followed re-

moval of the kidney and a solitary metastasis. Dr Barney\* had one case that was quite dramatic.

DR J DELLINGER BARNEY. I had a case with Dr Donald King some years ago in which the patient was suspected of having tuberculosis of the lung. X-ray study showed a mass in the lung about the size of an English walnut, which we first thought might be a tuberculoma. Later, a tumor of the kidney was discovered and removed, and then we decided that the lesion in the lung was probably a metastasis. It grew slowly and was not affected by x-ray therapy. During a long period of observation no other metastases appeared. It was decided that this probably was the only metastatic lesion that the patient had. Dr Churchill was asked to see her with the idea of removing it. He thought it could be done and did it. That was fourteen or fifteen years ago. I have not seen her recently, but Dr King has and says that she is not only alive but also very well, with no evidence of metastases elsewhere.

DR MALLORY. Have you anything to add, Dr King?

DR DONALD S KING. We have not had as much good luck in removing apparently solitary metastases in the lung as we hoped we might have. Several patients have had metastases to the brain that did not become manifest until the supposed single metastasis to the lung had come out.

\*Barney, J. D. Twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastases. *Tr Am A Genito-Urin Surgeons* 37:189, 1944.

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## —SUFFERETH LONG

THE time has come for a fresh appraisal of the various charitable undertakings of the country, at home and abroad, regarding both their needs and the means of supplying those needs. Scarcely a week now passes in which some special drive is not staged and a particular appeal presented, the demands are insatiable, the claims are constant, and some equitable method of assaying them and allocating to each its share of the available resources must be evolved.

In the Boston area a study is already on foot to analyze the expenditure in 1946 by tax-supported and voluntary agencies of \$88,000,000. This survey has received previous editorial comment in the *Journal*\*. More recently, at the joint annual meeting

of the Greater Boston Community Fund and the Greater Boston Community Council, the formation of a citizens committee to approve all the community's fund-raising appeals was recommended.

Already, and in steadily increasing numbers since the war ended, organizations are coming to the fore that make their independent solicitations for support, unrestricted by any acceptance of the quotas determined by the Community Fund. These appeals, on city, state and national levels, come from little known and scarcely recognized charities as well as from those country-wide associations, societies and foundations whose importance and whose authenticity are unquestioned. The success of their solicitations, however, is frequently based on their emotional appeal and perhaps sometimes on the extravagance of their suggestions rather than on the relative merits of the services they offer.

It will be readily admitted that the campaign for funds with which to study and treat infantile paralysis, as our most striking example makes a greater appeal and strikes more deeply into the pockets of the public than would any pleas for the where-withal with which to study arthritis, which cripples so many more victims. Many other of these independent organizations have also learned to dramatize their appeals in a way that does not always conform to even reasonable scientific accuracy. The American Cancer Society, for instance, when it states, in the course of its campaign for money, that 17,000,000 Americans will die of cancer "unless you do something about it" is presenting an unwarranted implication that enough American dollars can prevent all or most of the 17,000,000 deaths. Dollars are needed, true enough, but no guarantee of their purchasing power in terms of life should be implied. The public relations of the medical profession must be beyond reproach.

It seems apparent that the nation's money-raising enthusiasm should be tempered with sound judgment, that a fair appraisal of the merits of an appeal should be made and that money-raising activities should be conducted with the strictest candor and with a reasonable degree of co-ordination. The springs of private philanthropy may not run forever, but they will dry up less rapidly if their resources are pooled and properly dispensed.

\*Editorial: Greater Boston Community Service. *New Eng J Med* 238:340, 1948.



A local committee to approve publicly the fund-raising campaigns to be launched in a community will fill a needed want. A similar selective effort should be made regarding the larger organizations that operate on the grand scale. Our hearts go out to the citizens of Wichita, Kansas, referred to at the annual Community Fund and Community Council meeting, who conducted not long ago a "Leave Us Alone Week." It was the last bleat of the shorn lamb.

## BCG VACCINATION

THERE has been considerable discussion and interest in this country during the past two years in the use of BCG (*Bacillus Calmette Guérin*) vaccination as a means of immunization against tuberculosis. At a conference called in 1946 by the United States Public Health Service certain plans were formulated whereby a carefully controlled but well circumscribed study on a comparatively large scale could be carried out under the auspices of the Public Health Service. Because of growing interest in this subject, further seminars and conferences have been held in which the pros and cons of BCG vaccination were thrashed out by various experts in the field of tuberculosis. A summary of views of such experts was presented at a symposium sponsored recently by the National Tuberculosis Association.<sup>1</sup> Elsewhere in this issue of the *Journal* there is reprinted a statement of the present policy of the American Trudeau Society as submitted by the chairman of its chemotherapy committee and adopted by its executive committee. Finally, the views expressed at a conference called for that purpose in New York City last March were summarized by the chief of the Tuberculosis Control Division of the United States Public Health Service.<sup>2</sup>

It is clear from these reports and discussions that BCG vaccination is a safe procedure if used under proper supervision and in the proper circumstances. It has definite usefulness in many situations in which susceptible persons are exposed to infection, but its exact field of usefulness and limitation has not been fully defined. It is believed that to date there has been no reliable study of

sufficient duration to permit a precise evaluation of the effectiveness of vaccination over long periods. For that reason it was deemed unwise at present to make the BCG available for general distribution in this country.

Until the optimum methods of using this vaccine are defined and the exact field of usefulness and the limitations have been established, it seems best to limit its use and distribution to the controlled studies in which careful observations and prolonged follow-up examination by experts are possible. In this manner the best available information concerning the uses and limitations of BCG vaccination can be obtained and its field of usefulness can best be delineated.

In accordance with this policy plans for a BCG vaccination program in the city of Boston are under preparation by the Division of Tuberculosis of the Boston Health Department. Vaccine, according to recent advice from the Department, is to be furnished by the Tice Laboratory of Chicago, and the technical application of the program will be initiated by an associate of that laboratory and will be conducted as recommended in the report of the Chemotherapy Committee of the American Trudeau Society.

## REFERENCES

1. Sweeney, H. C., et al. Seminar on BCG. *Am Rev Tuberc* 57:95, 113, 1948.
2. Weber, F. J. Further study of BCG vaccination. *Pub Health Rep* 63:593, 1948.

## NURSE RECRUITMENT

THE National Student Nurse Recruitment Committee, with headquarters in Chicago, is soliciting the active co-operation of physicians in its current program. A national campaign is underway, and an enrollment goal of 50,000 new students in 1948 has been established.

An impressive list of sponsoring agencies includes the American Hospital Association, the American Medical Association, the American Red Cross, the American College of Surgeons and the United States Public Health Service.

A profession for women needs constant replenishment of ranks that are undergoing constant depletion. In other professions such as

medicine, law and engineering, engaged in largely by men, the majority of those embarking on these careers expect to continue in their practice throughout active life. Marriage acts only as an increased stimulus. Matrimony, on the other hand, attractive as it may seem in its various aspects, serves to curtail the years of active practice in a profession whose ranks are largely filled by women.

Despite aspersions that have been cast on the motives of hospitals in soliciting student-nurse enrollments, based on the assumption that these young women are being exploited in the interests of cheap labor—the hospital slave gangs of the la-di-da institutions, as Dr Brady, of the *Boston Traveler*, terms their training—the fact remains that wider horizons are opening up for the thoroughly trained nurse, in administration, in industry, in public health. Bedside nursing is another matter, and to care for the practical needs of the patient it is necessary that another type of nurse be trained according to a less ambitious program.

## MASSACHUSETTS MEDICAL SOCIETY

### ANNUAL GOLF TOURNAMENT

The winners at the annual golf tournament of the Massachusetts Medical Society, which was held at the Woodland Golf Club on the afternoon of May 26 and in which thirty-one physicians participated, were as follows: low gross, R. S. Nugent, low net, T. P. White, and second low net, J. Hammer.

### DEATHS

**GANLEY**—Edward H. Ganley, M.D., of Methuen died on January 23. He was in his fifty-seventh year. Dr. Ganley received his degree from Tufts College Medical School in 1917. He was a member of the staffs of Clover Hill and Lawrence General hospitals and was a fellow of the American Medical Association.

His widow, two sons and a daughter survive.

**SWEENEY**—Bartholomew P. Sweeney, M.D., of Leominster, died on May 20. He was in his sixty-second year.

Dr. Sweeney received his degree from Baltimore Medical College in 1911. He was a member of the American Urological Association and a fellow of the American Medical Association.

Two sons, a daughter and five grandchildren survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The July and August schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	July 7	William T. Green
Brockton	July 8	George W. Van Gorder
Salem	July 12	Paul W. Hugenberger
Gardner	July 13 and August 10	Carter R. Rowe
Worcester	July 16	John W. O'Meara
Springfield	July 20	Garry deN. Haugh, Jr.
Hyanus	July 22	Paul L. Norton
Fall River	July 26	David S. Grice
Lowell	August 6	Albert H. Brewster
Greenfield	August 9	Charles L. Sturdevant
Pittsfield	August 18	Frank A. Slowick

Physicians referring new patients to clinics should get in touch with the district health officer in making appointments. Patients are seen by appointment only.

### CLOSING DATE FOR AUTHORIZATION OF PAYMENTS IN EMERGENCY AND INFANT CARE PROGRAM

The federal Government has ruled that payment for maternity care may not be authorized after June 30, 1948, even though the patient was eligible for payment for such care prior to July 1, 1947.

If there are any such cases pending, the necessary application must be submitted at once to the office of the Department of Public Health, Division of Maternal and Child Health, 73 Tremont Street, Boston, to allow time to clear questions and to issue the authorization papers before June 30.

## MISCELLANY

### BCG VACCINATION

The following report was submitted to the Executive Committee of the American Trudeau Society, medical section of the National Tuberculosis Association at its meeting in Chicago on January 22, 1948, by Dr. H. McLeod Higgins of New York City, chairman of the Chemotherapy Committee and was adopted by the Executive Committee.

The members of the Society and other physicians in the United States have been interested for many years in active immunization against tuberculosis with BCG. The campaign of public-health activities in the field of tuberculosis control by official and voluntary agencies and the acquisition of new knowledge concerning immunity in tuberculosis have prompted the American Trudeau Society to make the following observations and recommendations:

BCG vaccine, prepared under ideal conditions and administered in tuberculin-negative persons by approved techniques, can be considered harmless.

The degree of protection reported following vaccination is by no means complete nor is the duration of induced relative immunity permanent or predictable. The need for further basic research on the problem of artificial immunization against tuberculosis is recognized and is to be emphasized. Studies should be directed toward the improvement of the immunizing agent, the development

of criteria for vaccination and revaccination and the more accurate determination of which groups in the general population should be vaccinated. Several well controlled studies are under way at the present time, and it is expected that others will begin in the near future.

On the basis of studies reported in the European and American literature, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of people who are likely to develop tuberculosis because of unusual exposure, inferior resistance, or both, are vaccinated.

In the light of present knowledge vaccination of the following more vulnerable groups of persons is recommended provided they do not react to adequate tuberculin tests: doctors, medical students and nurses who are exposed to infectious tuberculosis, all hospital and laboratory personnel whose work exposes them to contact with the bacillus of tuberculosis, persons who are unavoidably exposed to infectious tuberculosis in the home, patients and employees of mental hospitals, prisons and other custodial institutions in which the incidence of tuberculosis is known to be high, and children and certain adults considered to have inferior resistance and living in communities in which the tuberculosis mortality is unusually high.

Vaccination of the general population is *not* recommended at this time except for carefully controlled investigative programs, which, as a rule, will be best carried out under the auspices of official agencies such as the United States Public Health Service, state and municipal health departments and other especially qualified groups.

BCG vaccine should not be made available for general distribution in the United States at present because the most effective strain of BCG has not been agreed upon nor has fully satisfactory standardization of the vaccine been achieved, the best qualified experts have not agreed about the most effective method of vaccination, and fully satisfactory arrangements have not been perfected for transportation and storage of the vaccine.

The vaccine should be prepared only in accredited laboratories especially devoted to this task, in which virulent tubercle bacilli are not cultivated or handled and in which all other possible precautions are exercised to assure safety and quality of the product.

Adequate record systems should be devised for management of the statistical problems involved in recording and following large numbers of vaccinated people. These and other problems of particular importance are now being studied on an extensive scale by official and voluntary agencies in the United States and in close collaboration with European scientists experienced in this field.

The Society believes that since BCG vaccination affords only incomplete rather than absolute protection, the most effective methods of controlling tuberculosis in the general population are further improvement of living conditions and general health, reduction of tuberculous infection, which can be accomplished by modern public-health methods and the unremitting search among presumably healthy persons for patients with infectious tuberculosis, prompt and adequate medical and surgical treatment of patients with active disease, segregation and custodial care of those not amenable to accepted forms of therapy and adequate rehabilitation.

Fortunately, great advances have been achieved during recent years in the development of diagnostic methods applicable on a mass scale, and there have been significant improvements in the surgical and medical treatment of tuberculosis. The expansion of modern diagnostic, therapeutic and rehabilitation facilities is required to make full use of these new methods, which can accomplish further dramatic reduction of tuberculosis mortality and morbidity in the United States.

It is to be emphasized that BCG vaccination must not be regarded as a substitute for approved hygienic measures or for public-health practices designed to prevent or minimize tuberculous infection and disease. Vaccination should be regarded as only one of many procedures to be used in tuberculosis control. Vaccination seems unwarranted in areas in which the tuberculosis mortality rate is extremely low and in localities in which the tuberculin test is of especial value as a differential diagnostic procedure.

## CORRESPONDENCE

### CORRECT DOSAGE OF CURARE

*To the Editor* I should like to call your attention to an error in the designated d-tubocurarine chloride content of the oil and myrcin preparation in the article by Drs Kuhn and Bickers, entitled "An Evaluation of Curare in Spasticity due to Spinal-Cord Injuries," which appeared in the April 29 issue of the *Journal*. The amount as given, 175 mg of d-tubocurarine chloride (per cubic centimeter), should be changed to 175 units of d-tubocurarine chloride (per cubic centimeter), the actual weight of d-tubocurarine chloride is about 27 mg per cubic centimeter in d-tubocurarine chloride in oil and myrcin (Squibb).

This error is a natural one, arising from the use of milligrams and units interchangeably by clinicians in references to curare dosage of intocostin in the literature, because in the development of this product the unit was originally defined as the curare activity equivalent to that of 1 mg of a particular curare powder previously employed as the standard. The physiologic activity of 1 unit of curare activity is still essentially the same, but 1 unit is now designated as the curare activity equivalent to that of 0.15 mg of crystalline d-tubocurarine chloride (pentahydrate form). Since, on this unitage basis, 10 mg of d-tubocurarine chloride (pentahydrate) has about 66 units of curare activity, it would be exceedingly dangerous to interchange units and milligrams when one refers to the dosage of this compound either in aqueous solutions or in oil-wax preparations.

CHARLES R. LINEGAR, Ph.D., *Director*  
Pharmacological Development Division

E. R. Squibb and Sons  
New Brunswick, New Jersey

### SKEPTICISM ON VENEREAL-DISEASE CONTROL

*To the Editor* The editorial entitled "Venereal-Disease Control," which appeared in the May 27 issue of the *Journal*, praises "the remarkable drop in the incidence of venereal disease during 1947" in the United States Army.

Perhaps I am quite mistaken, but I tend to view with considerable skepticism any report that venereal-disease rates could be decreased 40 or 50 per cent by any "intelligent appeal to the higher moral sense of the individual," and although I realize that you are much better informed than I am on this subject, I hesitate to share your enthusiasm for the new program. Before I agree with your viewpoint I would like to know how much of the venereal disease that is occurring in the Army at present is actually being reported and treated by the Army. In view of an increased rate of venereal disease treated by civilian doctors during the same period one is inclined to question just how many of the Army's patients with venereal disease are being driven to civilian doctors by the so-called "new program."

Although I was in the Navy and not the Army during the past war, the efforts of the armed forces to deal frankly and openly with the venereal-disease problem seemed very encouraging, and the training films were an outstanding contribution to both prevention and control. Although I agree with you that moral and spiritual factors should not be overlooked in syphilis, I feel that overemphasis combined with punishment of any form will only serve to drive the disease "underground" and undo all the fine work done by medical officers during the war.

On more than one occasion during the war various units of the armed forces made similar claims in reduction of venereal disease by means of "appeals to morals," which were backed by various means of punishment of the unfortunate soldiers who were victims of the disease. In several cases it was discovered, however, that local doctors were doing a rushing business in treatment of servicemen who did not dare to report their infections.

Are you sure that the Army has made a step forward?

E. M. KNIGHTS, JR., M.D.  
Providence, Rhode Island

Note: The information on which the above-mentioned editorial was based was derived from the office of the Surgeon General among other sources. — Ed

(Notices on page xv)

# NOTICES

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING  
THURSDAY, JULY 1

FRIDAY JULY 2

\*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital

TUESDAY JULY 6

\*12:00 m. (A-24) Conference Margaret Jewett Hall, Mt. Auburn Hospital Cambridge

\*12:15-1:15 p.m. Cytogenetiological Conference Peter Bent Brigham Hospital

\*1:30-2:30 p.m. Pediatric Rounds Barnham Memorial Hospital for Children Massachusetts General Hospital

WEDNESDAY JULY 7

\*12:00 m.-1:00 p.m. Clinical Conference (Children & Hospital) Amphibtheater Peter Bent Brigham Hospital

\*Open to the medical profession

JUNE 25 and 26. Christian Medical Society Page 492, issue of April 1

JUNE 28-30 American Academy of Pediatrics. Hotel Schroeder Milwaukee Wisconsin

JUNE 28-JULY 23 Harvard Seminar on Health Education Page 856, issue of June 10.

JULY 6-24 Students International Clinical Congress. Page 455 issue of March 25

JULY 12-17 First International Polymyositis Conference. Page 36, issue of January 1

AUGUST 11-21 International Congress on Mental Health Page 344 issue of March 4.

AUGUST 23-26. International Society of Hematology Page 419 issue of March 18.

AUGUST 26-28 American Association of Blood Banks. Page 420, issue of March 18.

SEPTEMBER 7-11 American Congress of Physical Medicine Page 582 issue of April 15

SEPTEMBER 13-15 American Academy of Pediatrics. Olympic Hotel, Seattle, Washington

SEPTEMBER 16-18 Vermont State Medical Society Annual Meeting Burlington.

SEPTEMBER 20-23 American Hospital Association Page 310 issue of February 26.

SEPTEMBER 29, Mississippi Valley Medical Editors Association Page 170 issue of January 29

OCTOBER 6-9 American Board of Ophthalmology Page 170 issue of January 29

OCTOBER 27 New England Obstetrical and Gynecological Society Annual Meeting. Hotel Somerset Boston

NOVEMBER 1-3 American Clinical and Climatological Association Page 582 issue of April 15

NOVEMBER 8-12 American Public Health Association Page 420 issue of March 18.

NOVEMBER 10-13 Association of Military Surgeons of the United States. Page 722 issue of May 13

NOVEMBER 20-23 American Academy of Pediatrics Annual Meeting Chalfonte Haddon Hall Hotel Atlantic City New Jersey

DECEMBER 7-9 Southern Surgical Association Annual Meeting Page 543 issue of April 8.

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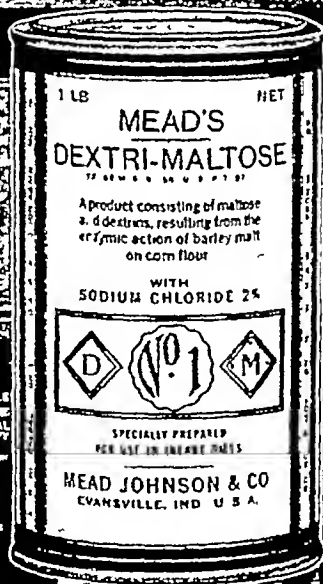
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